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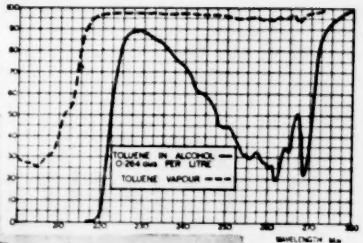


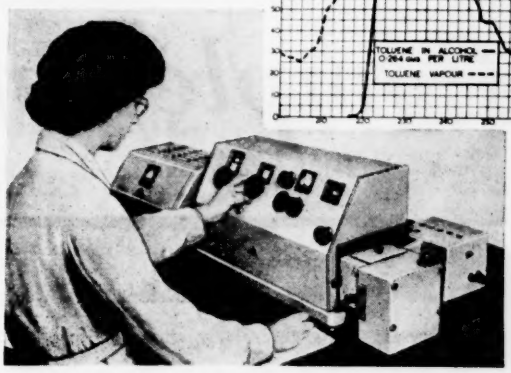

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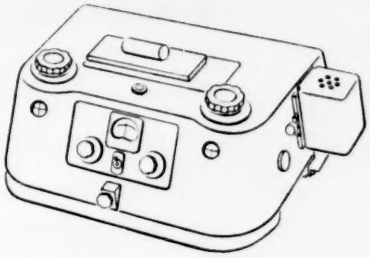

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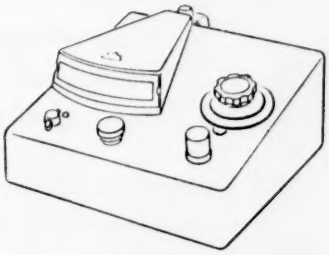

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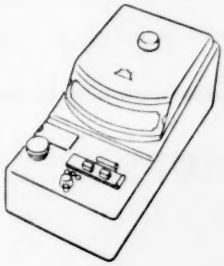

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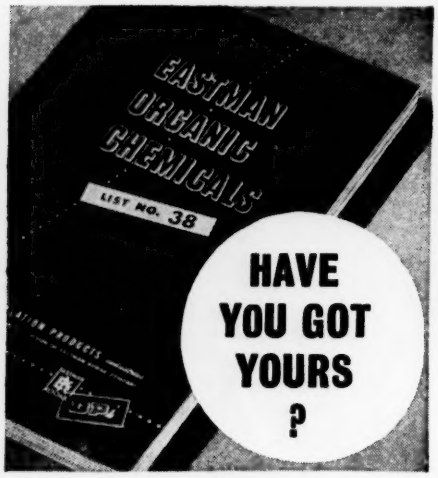


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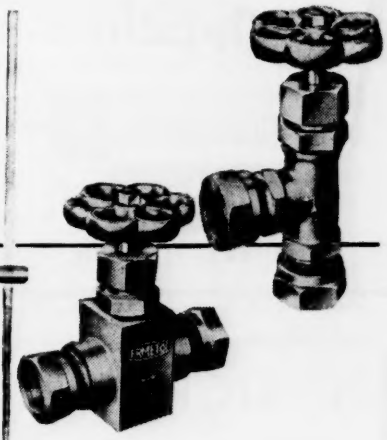

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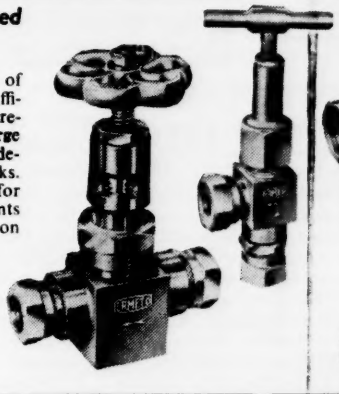

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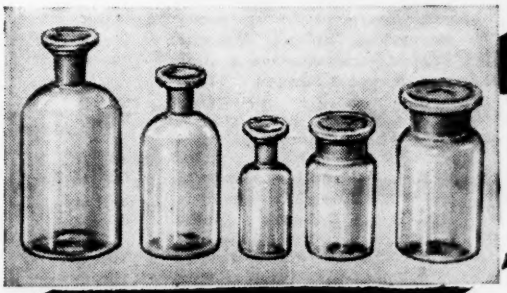

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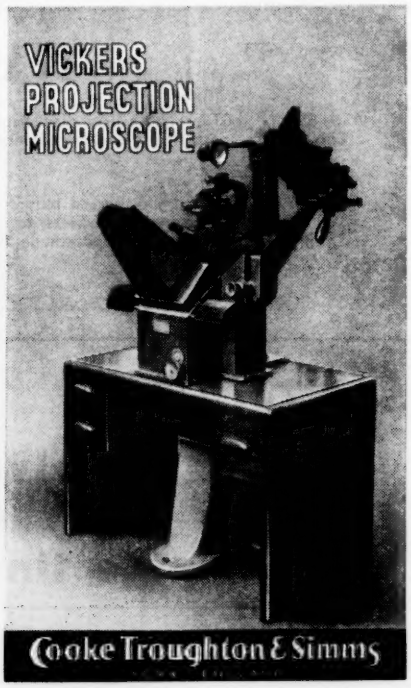


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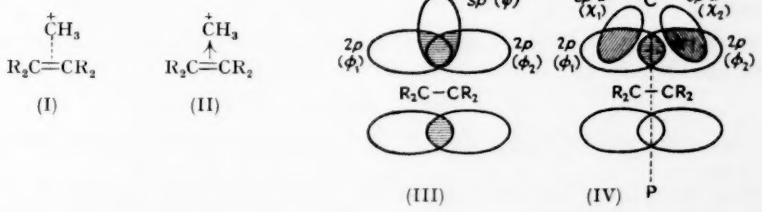
# 576. *The Role of* 3d-*Electrons in Valency States of First-row Elements.*

By M. J. S. Dewar.

Gillespie (*J.*, 1952, 1002) has suggested that 3*d*-orbitals may contribute to valency states of carbon in certain electron-deficient compounds. It is now shown that any such contributions leave the general configuration of the valency electrons unchanged.

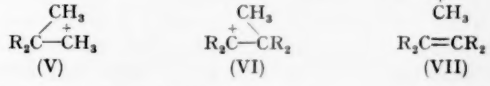
Gillespie (*J.*, 1952, 1002) recently suggested that 3*d*-orbitals may contribute to certain valency states of first-row elements in general, and of carbon in particular. In the present paper the problem is investigated in more detail and it is shown that a flaw in Gillespie's argument invalidates most of his conclusions.

The point can be made most clearly by referring to one of the specific problems discussed by Gillespie: the structure of the triangular non-classical ion (I), derived from $CH_3^+$ and a symmetrical olefin. Structures of this type appear as intermediates in carbonium-ion rearrangements (cf. Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3274), and they have been interpreted (Dewar, *J.*, 1946, 406) as co-ordination compounds ($\pi$-complexes) of the olefin acting as donor to the alkyl cation as acceptor, as in (II). According to this view the two electrons taking part in the dative bond occupy a molecular orbital formed from the 2*p* atomic orbitals that contribute to the $\pi$-bond of the olefin, and a single tetrahedral, hybrid atomic orbital of the methyl carbon atom. (This is equivalent to earlier representations in terms of resonance theory; see Dewar, *Bull. Soc. chim.*, 1951, **18**, 71C, for a review and references.) The orbitals concerned, and their mode of overlap, are indicated in (III). Gillespie now suggests that the orbitals of the methyl group involved in the formation of (I) are not a single $sp^3$ hybrid as in (III), but a pair of $sp^3d$ hybrids ($\chi_1$, $\chi_2$) (IV) formed by further hybridisation of the tetrahedral $sp^3$ atomic orbital with a 3*d* atomic orbital. His argument is that the difference in energy between the $sp^3$ atomic orbital and an unoccupied 3*d* atomic orbital of carbon is small enough to allow interaction, and that the resulting $sp^3d$ atomic orbitals can overlap much more efficiently with the olefinic *p* orbitals than can the single $sp^3$ hybrid.




(I) (II) (III) (IV)

Gillespie did not analyse the fate of the two electrons that bond the three carbon atoms in (I). It is evident that no one of the three possible classical structures (V)—(VII), corresponding to the possible modes of overlap in (IV), can represent the system; it must be depicted as a hybrid of these structures, possibly with others in addition. The flaw




(V) (VI) (VII)

in Gillespie's argument lies in the fact that when the system is so depicted, the net contribution of the 3*d* orbital vanishes identically. Gillespie's suggestion, although at first sight attractive, is therefore fundamentally incorrect. The same flaw invalidates his con-

clusions concerning other electron-deficient systems (beryllium, aluminium, and platinum methyls); here again carbon 3*d* orbitals cannot be involved in the way Gillespie suggested.

The valence-bond treatment of this system is relatively complicated and involves factors not considered by Gillespie. The problem will therefore first be discussed in terms of molecular-orbital theory, wherein the possible role of the 3*d* orbitals will become clearer. The results obtained also serve as a guide in the subsequent valence-bond treatment of (I).

It will be assumed throughout that the normal σ-bonds in (I), *i.e.*, the C–H and C–R bonds, and the σ-component of the $R_2C$–$CR_2$ bond, are formed by localised pairs of electrons; this conventional assumption is reasonable since any delocalisation of the σ-electrons can lead only to small second-order effects (*i.e.*, hyperconjugation). It will also be assumed * (cf. Dewar, *loc. cit.*) that the $R_2C{\cdot}CR_2$ group in (I) is coplanar, the central pair of carbon atoms having $sp^2$ hybridisation, and that the methyl-carbon atom lies on the two-fold axis of symmetry perpendicular to the plane containing the groups R. The two carbon atoms, C, in the grouping $R_2C{\cdot}CR_2$ will be referred to as the *basal* carbon atoms, and that in the methyl group as the *apical* carbon atom. With these assumptions, (I) has two planes of symmetry: one (*P*) perpendicular to the line joining the basal carbon atoms, and one (*Q*) containing the basal and the apical carbon atoms [see (IV)]. These three carbon atoms are linked by a delocalised pair of electrons, and it is the configuration of these electrons that is to be studied.

In the molecular-orbital representation, this pair of electrons occupies a single molecular orbital. The atomic orbitals available for constructing this are the two unhybridised 2*p* orbitals [$\phi_1$, $\phi_2$ in (IV)] of the basal carbon atoms, and an $sp^3$ hybrid orbital ($\psi$), and the set of five 3*d* orbitals, of the apical carbon atom.

Since these five 3*d* orbitals form a complete set, there is no loss in generality if an arbitrary orthogonal set is chosen; for any 3*d* orbital of the apical carbon atom will be expressible as a linear combination of orbitals from any such set. The usual choice, which will be quite suitable here, is a set of five real orbitals defined with respect to cartesian co-ordinates. For the present purpose it will be convenient to arrange the orbitals so that each is either symmetric or antisymmetric with respect to inversion in either of the planes *P*, *Q*. Accordingly the intersection of *P* and *Q* is taken to be *z*-axis, *P* the *yz*-plane, and *Q* the *xz*-plane. The symmetry properties of the corresponding set of 3*d* orbitals are shown in the Table. The orbital explicitly considered by Gillespie is the one described here as $3d_{xz}$.

| Orbital | | $3d_{xy}$ | $3d_{xz}$ | $3d_{yz}$ | $3d_{x^2-y^2}$ | $3d_{z^2}$ | $\phi^+$ | $\phi^-$ | $\psi$ |
|---|---|---|---|---|---|---|---|---|---|
| Behaviour on reflection in | *P* | — | — | + | + | + | + | — | + |
| | *Q* | — | + | — | + | + | + | + | + |

The orbitals $\phi_1$, $\phi_2$ do not conform to the symmetry of the molecule, and it is convenient to replace them by an equivalent pair of "symmetry orbitals" $\phi^+$, $\phi^-$ defined by

$$\phi^+ = 2^{-\frac{1}{2}}(\phi_1 + \phi_2);\ \phi^- = 2^{-\frac{1}{2}}(\phi_1 - \phi_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The symmetry properties of $\phi^+$ and $\phi^-$, and of the $sp_3$ hybrid orbital $\psi$, are also shown in the Table.

Now the average electron distribution in a molecule must conform to the symmetry of the field in which the electrons move. Since the nuclear field in (I) is symmetric with respect to reflection in *P* and *Q*, so also must be the average electron distribution. Consequently the wave function of the electrons must be either symmetric or antisymmetric, the electron distribution being symmetric in either case since it is given by the square of the wave function. The required three-centre molecular orbital Φ must therefore be either symmetric or antisymmetric with respect to reflection in *P*, *Q*. But Φ is being constructed from orbitals each of which has that kind of symmetry; it is then easily seen that Φ will be of the required type only if it is composed of orbitals all of exactly the same symmetry type.

Since moreover at least one of the orbitals $\phi^+$, $\phi^-$ must contribute to Φ if electrons in Φ are to bond all three carbon atoms C in (I), and since both $\phi^+$ and $\phi^-$ are symmetric with respect to reflection on *Q* (see Table), the orbitals $3d_{xy}$, $3d_{yz}$ cannot contribute to Φ. The

* This assumption does not affect the argument that follows; $\phi_1$, $\phi_2$ [in (IV)] could equally be hybrid orbitals.

remaining orbitals can be classified as symmetric or antisymmetric depending on their behaviour on reflection in $P$:

| | | |
|---|---|---|
| Symmetric | $3d_{x^2-y^2}$, $3d_{z^2}$ | (2) |
| Antisymmetric | $3d_{xz}$ | |

$\Phi$ must be represented as a linear combination of orbitals from one or other of these sets, but not both.

It is evident that the molecular orbital of lowest energy (*i.e.*, $\Phi$) will be symmetric, for the lowest symmetric orbital will have no nodes, whereas the lowest antisymmetric orbital necessarily has one node (in the plane $P$). Moreover, the low-energy atomic orbital $\psi$ can contribute only to symmetric molecular orbitals. Therefore the only $3d$ orbitals that can contribute to $\Phi$ are the symmetric orbitals $3d_{x^2-y^2}$ and $3d_{z^2}$.

This immediately disposes of Gillespie's suggestion that the bonding of the apical carbon is through hybrids of $\psi$ with the antisymmetric orbital $3d_{xz}$. The latter orbital cannot contribute at all to the ground state of (I). Contributions by the symmetric $3d$ orbitals, while possible, would not alter the general situation; for hybrids of such orbitals with $\psi$ would have the same general shape as $\psi$ itself and would not overlap any better than $\psi$ with the basal $p$ orbitals $\phi_1$, $\phi_2$. Whether or not these symmetric $3d$ orbitals do in fact make a significant contribution to the ground state of (I) is a question which could be answered only by detailed calculations of prohibitive difficulty. On general grounds it seems very unlikely that such contributions can be appreciable in view of the high energy of the $3d$ orbitals and in view of the fact that their inclusion would not increase the orbital overlap. But the type of $d$ orbital hybridisation considered by Gillespie is definitely ruled out by considerations of symmetry.

The valence-bond representation will now be discussed. The structure (I) is then depicted as a hybrid of the structures (V), (VI), and (VII). According to Gillespie, the C–$CH_3$ bond in (V) or (VI) is formed through a $sp^3d$ hybrid orbital of the apical carbon atom. The $d$ component of this orbital can be represented as a linear combination of the standard $d$ orbitals (see Table). If $t$ is written for the relevant $sp^3$ orbital of the apical carbon atom, the bonds are then formed by $td^5$ hybrid orbitals of that atom.

Now if the C–$CH_3$ bond in (V) is formed by such a hybrid, (V) can in turn be represented as a hybrid of the six structures (VIII) in each of which the C–$CH_3$ bond is formed by one or other of the six " pure " orbitals ($t$ or $d$). Likewise, (VI) can be represented as a hybrid of the six structures (IX). ($T$, $D_{xy}$, etc., denote structures derived from the atomic orbitals $t$, $d_{xy}$, etc.).

$$\begin{array}{c} \mathrm{CH_3} \\ \diagup \\ \mathrm{R_2C{-}\overset{+}{C}R_2} \\ T,\ D_{xy},\ D_{yz},\ D_{xz},\ D_{x^2-y^2},\ D_{z^2} \\ \text{(VIII)} \end{array} \qquad \begin{array}{c} \mathrm{CH_3} \\ \diagdown \\ \mathrm{R_2C{-}\overset{+}{C}R_2} \\ T',\ D_{xy}',\ D_{yz}',\ D_{xz}',\ D_{x^2-y^2}',\ D_{z^2}' \\ \text{(IX)} \end{array}$$

The bond eigenfunctions $\Phi$, $\Phi'$ of (V) and (VI) are then given by

$$\left.\begin{aligned} \Phi &= aT + \sum_r b_r D_r \\ \Phi' &= a'T' + \sum_r b_r' D_r' \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (3)$$

and the total eigenfunction $\Psi$ of (I) by

$$\begin{aligned} \Psi &= c\Phi + c'\Phi' + c''\Phi'' \\ &= (acT + a'c'T') + \sum_r (b_r c D_r + b_r' c' D_r') + c''\Phi'' \quad \ldots\ldots \quad (4) \end{aligned}$$

where the $a$'s, $b$'s, and $c$'s are algebraic coefficients and $\Phi''$ is the bond eigenfunction of (VII).

Now $\Psi$ must be either symmetric or antisymmetric with respect to inversion in $P$; it follows that

$$ac = \pm a'c';\ b_r c = \pm b_r' c' \quad \ldots\ldots\ldots \quad (5)$$

Therefore, (4) can be written in the form

$$\Psi = m(T \pm T') + \Sigma_r n_r(D_r \pm D_r') + c''\Phi'' \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The structures $T$, $D_r$, etc., can therefore enter $\Psi$ only as the " symmetry eigenfunctions " $(T \pm T')$, $(D_r \pm D_r')$. Also for reasons given earlier, all the contributing symmetry eigenfunctions must be of the same symmetry type, and since $\Phi''$ is itself symmetric it can contribute only if $\Psi$ is symmetric.

Let us denote the twelve symmetry eigenfunctions by $(X_r \pm X_r')$, derived from atomic orbitals $\xi_r$ where $\xi_r$ is $t$ or one of the five $3d$ orbitals. $(X_r \pm X_r')$ can be factored into a series of products of $\sigma$-bond eigenfunctions, a spin term for the pair of electrons forming the central C–C bonds, and the corresponding space eigenfunction. Since the two former sets of factors will be common to all the functions in $\Psi$, attention can be confined to the space eigenfunction of the delocalised pair of electrons. In the case of $(X_r + X_r')$ and $(X_r - X_r')$ these functions, $x_r$, $x_r'$ can be expanded as

$$\left.\begin{aligned} x_r &= 2^{\frac{1}{2}}\{(\phi_1{}^1\xi_r{}^2 + \phi_1{}^2\xi_r{}^1) + (\phi_2{}^1\xi_r{}^2 + \phi_2{}^2\xi_r{}^1)\} \\ &= 2^{\frac{1}{2}}\{(\phi_1{}^1 + \phi_2{}^1)\xi_r{}^2 + (\phi_1{}^2 + \phi_2{}^2)\xi_r{}^1\} \\ x_r' &= 2^{\frac{1}{2}}\{(\phi_1{}^1\xi_r{}^2 + \phi_1{}^2\xi_r{}^1) - (\phi_2{}^1\xi_r{}^2 + \phi_2{}^2\xi_r{}^1)\} \\ &= 2^{\frac{1}{2}}\{(\phi_1{}^1 - \phi_2{}^1)\xi_r{}^2 + (\phi_1{}^2 - \phi_2{}^2)\xi_r{}^1\} \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where the superscripts as usual distinguish between the electrons occupying the various atomic orbitals. From (7) it is seen that $x_r$, $x_r'$ have the form of simple bond eigenfunctions for bonds formed between the atomic orbital $\xi_r$ and the symmetry orbitals $\phi^+$, $\phi^-$ [cf. eqns. (1)]. Now a bond can be formed by two orbitals only if they have the same symmetry. Since $\phi^+$ and $\phi^-$ are symmetric with respect to inversion in $Q$, only those symmetry eigenfunctions can contribute to $\Psi$ which are derived from orbitals $\xi_r$, symmetric with respect to inversion in $Q$. Consequently the symmetry eigenfunctions derived from the orbitals $3d_{xy}$ or $3d_{yz}$ can be eliminated at once, since they do not correspond to structures with a bond between the apical carbon and one basal carbon atom. Of the remaining pairs of symmetry eigenfunctions $(X_r \pm X_r')$, only one in each case is acceptable for the same reason. The surviving eigenfunctions may now be classified according to their behaviour on reflection in $P$:

$$\left.\begin{aligned} &\text{Symmetric} \quad (T + T'),\ (D_{x^2-y^2} + D'_{x^2-y^2}),\ (D_{z^2} + D_{z^2}') \\ &\text{Antisymmetric} \quad (D_{xz} + D_{xz}') \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Since the functions contributing to $\Psi$ must be either all symmetric or all antisymmetric, it is evident that $(T + T')$ and $(D_{xz} + D_{xz}')$ cannot both contribute. Consequently the relevant orbitals of the apical carbon atom in (I) cannot be $td_{xz}$ hybrids, as Gillespie supposed.

It is evident that the ground state of (I) must be symmetric, not only because many more structures can contribute to a symmetric state, but also because the symmetric structures include $(T + T')$ and $\Phi''$ which must on energetic grounds be the most important. Both the molecular-orbital and valence-bond treatments agree on this point, and a comparison of expressions (2) and (6) shows that they also agree on the orbitals which can contribute to (I), on the orbitals which can contribute to symmetric states of (I), and on the orbitals which can contribute to antisymmetric states.

The difficulty in applying the valence-bond method to this problem lies in distinguishing between pairs of symmetry eigenfunctions $(X_r + X_r')$ and $(X_r - X_r')$. One or other member of each pair will be symmetric with respect to inversion in $P$, and it is not at all evident why each symmetric member should not be able to contribute to $\Psi$.

The argument given above shows, however, that one member of each pair must be rejected since it does not correspond to a bonded structure. The flaw in Gillespie's argument is evident; his structures for (V) and (VI) correspond in the present terminology

(neglecting algebraic factors) to $(T + D_{zz})$ and $(T' - D_{zz}')$; the final eigenfunction $\Psi$ for (I) then reduces (numerical factors being neglected) to

$$\Psi'' = (T + T') + (D_{zz} - D_{zz}') + \Phi'' \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and the contribution of the second term in fact vanishes.

These arguments may easily be extended to the other electron-deficient molecules considered by Gillespie, in particular beryllium, aluminium, and platinum methyls. In each case there can be no contribution to the ground state by the particular *d* orbitals invoked by him. The only *d* orbitals that can contribute are ones which do not significantly alter the symmetry of the tetrahedral $sp^3$ orbitals with which hybridisation is supposed to occur, and such contributions cannot therefore have any significant effect on the efficacy of orbital overlap.

It may be noted that these criticisms of Gillespie's suggestions do not apply to systems containing additional electrons. Thus the transition state of a Stevens rearrangement formally resembles (I), but with $CH_3^-$ replacing $CH_3^+$; here there are two additional delocalised electrons which must occupy a molecular orbital of higher energy than $\Phi$. Of the two lowest orbitals available, one is in fact antisymmetric with respect to inversion in *P*. If the extra electrons occupy this orbital, a contribution by the $3d_{zz}$ orbital would be possible. The same is true of the transition state for a $S_N2$ reaction where two of the four delocalised electrons occupy an orbital of symmetry appropriate to *d* interaction. Note that in these cases classical structures are not electron-deficient; in the case of (I), or of the metal methyls mentioned above, at least one atom has an incomplete valency shell in any classical structure.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, October 31st*, 1952.]

## 577. *The Reaction of Diazonium Salts with β-2-Thienylacrylic Acid.*

By WALTER FREUND.

Under Meerwein's conditions (Meerwein, Buchner, and van Emster, *J. pr. Chem.*, **1939**, **152**, 237) β-2-thienylacrylic acid and *p*-nitrobenzenediazonium chloride give only a small amount of 5-*p*-nitrophenyl-2-4′-nitrostyrylthiophen, but with other diazo-compounds the 2-styrylthiophens are obtained; β-2-furylacrylic acid generally gives the diarylated compounds. The differing reactions of thiophen- and furan-acids are considered to favour the assumption of an ionic reaction mechanism.

FROM the reaction of diazonium salts with β-2-furylacrylic acid three classes of compounds were obtained, *viz.*, 5-aryl-2-styrylfurans, showing strong fluorescence in organic solvents, α-(5-aryl-2-furyl)acrylic acids, and 2-styrylfurans (Freund, *J.*, **1952**, **3068**), whereas the last were the only reaction products to be expected according to Meerwein, Buchner, and van Emster (*J. pr. Chem.*, **1939**, **152**, 237). It appeared of interest to investigate whether double arylation, previously only encountered with quinones (G.P. **508,395**; Kvalnes, *J. Amer. Chem. Soc.*, **1934**, **56**, 2478), would take place with compounds similar to furylacrylic acid. β-2-Thienylacrylic acid underwent arylation under Meerwein's conditions (*loc. cit.*) with great ease, but with diazotised *p*-nitroaniline yielded only a small amount of 5-*p*-nitrophenyl-2-4′-nitrostyrylthiophen, which showed a green fluorescence in benzene similar to that of the corresponding furan compound. Such strong arylating agents as diazotised *p*-chloroaniline and *p*-aminobenzoic acid gave only 2-4′-chloro- and 2-4′-carboxy-styrylthiophen. It appears difficult to reconcile the different behaviour of β-2-furyl- and β-2-thienyl-acrylic acid with the claim that in the Meerwein reaction organic radicals are involved (Waters, *J.*, **1946**, 411; "The Chemistry of Free Radicals," London, 1946; cf. Freund, *loc. cit.*). Polarisation of the double bonds seems to be the dominating factor as suggested by Meerwein *et al.* (*loc. cit.*).

## Experimental

*β-2-Thienylacrylic Acid.*—Perkin condensation with thiophen-2-aldehyde according to Biedermann (*Ber.*, 1886, **19**, 1855) gave only a very poor yield of thienylacrylic acid. Doebner condensation (1 mol. of the aldehyde and 2 mols. of malonic acid in pyridine with a few drops of piperidine) gave the acid, m. p. 147—148°, in 70% yield (Cohn, *Z. physiol. Chem.*, 1893, **17**, 283; m. p. 144—145° : Nord, *J. Org. Chem.*, 1949, **14**, 409).

*2-4′-Carboxystyrylthiophen.*—A filtered diazonium solution, prepared from *p*-aminobenzoic acid (6·85 g.), sodium nitrite (3·7 g.) in water (40 c.c.), 25% hydrochloric acid (20 g.), and water (70 c.c.), was added to β-2-thienylacrylic acid dissolved in acetone (150 c.c.) in which crystalline sodium acetate (20 g.) was suspended. After the pH had adjusted itself to approx. 6, the mixture was warmed to 28—30° and a solution of copper chloride (1·5 g.) in water (10 c.c.) was added. Gas evolution was rapid at 30° and lasted for about 1 hr. After removal of the acetone a solid resin remained which was extracted with dilute aqueous ammonia. Approx. 4 g. of buff-coloured material remained. This dissolved in hot dilute alkali and crystallised from acetic acid from which the *2-4′-carboxystyrylthiophen* separated in globuli, m. p. 251—254° (Found : C, 67·8; H, 4·5; S, 13·8. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·4; S, 13·9%).

The ammoniacal solution was acidified and the precipitate boiled with water to remove unchanged β-2-thienylacrylic acid. Some brown material remained which after digestion with a small amount of cold alcohol was recrystallised from alcohol. The poorly developed brown crystals melted at 270—280°. This compound has not yet been closely investigated; it may be α-*p*-carboxyphenyl-β-2-thienylacrylic acid.

*2-4′-Chlorostyrylthiophen.*—A diazonium solution from *p*-chloroaniline (6·4 g.), sodium nitrite (3·65 g.), 25% hydrochloric acid (22 c.c.), and ice (10 g.) was filtered and added to a solution of β-2-thienylacrylic acid (7·7 g.) in acetone (150 c.c.) in which sodium acetate (20·22 g.) was suspended. The pH of the mixture was approx. 6. On addition of copper chloride (2 g.) in water (10 c.c.) gas evolution set in which lasted for about 40 min. After removal of the acetone the residue was extracted with dilute ammonia. Two recrystallisations of the residue (4 g.) from alcohol gave prisms of *2-4′-chlorostyrylthiophen*, m. p. 137° (Found : C, 65·2, 65·1; H, 4·5, 4·3; Cl, 16·1; S, 14·5. $C_{12}H_9SCl$ requires C, 65·3; H, 4·1; Cl, 16·1; S, 14·5%). The ammoniacal solution on acidification gave only unchanged thienylacrylic acid.

*2-4′-Nitrostyrylthiophen.*—*p*-Nitroaniline (13·8 g.) was diazotised and the filtered solution added to one of β-2-thienylacrylic acid (15·4 g.) in acetone (200 c.c.) in which sodium acetate (*ca.* 45 g.) was suspended. Gas evolution set in immediately and became violent on the addition of a solution of copper chloride (5 g.) in water (10 c.c.); it was over in a few minutes. The mass of crystals was filtered off (filtrate *A*), washed with dilute aqueous ammonia and cold ethanol, and dried in a desiccator (yield, 7 g.). This was boiled with alcohol (400 c.c.) in which 1·5 g. (substance *B*) remained undissolved. The alcoholic solution, on cooling, yielded yellowish crystals (6·9 g.), m. p. 168—169°. These were passed in benzene through alumina and once more recrystallised, yielding *2-4′-nitrostyrylthiophen*, needles, m. p. 174° (Found : C, 61·8, 61·9; H, 4·0, 4·0; N, 6·0, 5·8; S, 13·6. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9; N, 6·1; S, 13·9%).

*5-p-Nitrophenyl-2-4′-nitrostyrylthiophen.*—Substance *B* was twice recrystallised from glacial acetic acid and then melted (const.) at 220—222°. It was passed in benzene through alumina where a dark brown impurity was removed. The substance crystallised in short scarlet prisms from the concentrated benzene solution; from glacial acetic acid, *5-p-nitrophenyl-2-4′-nitrostyrylthiophen* crystallised in red needles or prisms, m. p. 232°, and showed in benzene a strong yellow-green fluorescence (Found : C, 62·2; H, 3·8; N, 8·6; S, 9·3. $C_{18}H_{12}O_4N_2S$ requires C, 61·3; H, 3·4; N, 8·0; S, 9·1%).

Filtrate *A* was subjected to steam-distillation which removed the acetone and some *p*-chloronitrobenzene. The dark residue (*C*) was digested with dilute aqueous ammonia, and the solution filtered. On acidification a solid was precipitated which was repeatedly extracted with boiling water to free it from unchanged thienylacrylic acid, and then dried on a porous plate. After recrystallisations from alcohol and acetic acid, olive needles, m. p. 235—238°, were obtained. The *p*-nitrophenyl group may have entered position 5 of the thiophen nucleus or the α-position of the side chain. The latter constitution is tentatively suggested, namely, *α-p-nitrophenyl-β-2-thienylacrylic acid* (Found : C, 56·4, 56·3; H, 3·5, 3·5; N, 5·2, 5·0; S, 11·5, 11·6. $C_{13}H_9O_4NS$ requires C, 56·7; H, 3·3; N, 5·1; S, 11·6%).

The residue *C* (after the ammoniacal extraction; approx. 7·2 g.) was dried and twice

recrystallised from ethanol and acetic acid, and 1·5 g. of still impure 2-*p*-nitrostyrylthiophen were obtained.

2-4′-*Aminostyrylthiophen*.—2-4′-Nitrostyrylthiophen (m. p. 168—169°; 4·4 g.) was gradually introduced into a solution of anhydrous stannous chloride in glacial acetic acid (55 c.c.) (240 g. of $SnCl_2$ in 500 c.c. of acid), saturated with dry hydrochloric acid, and stirred for 3 hr. at 35°, left overnight, and then filtered. The precipitate was washed with a little acetic acid and decomposed with 25% aqueous sodium hydroxide (130 c.c.) under external and internal cooling with ice. The solid material was filtered off, washed until neutral with water, dried in a desiccator, and extracted with benzene. The solution was passed through alumina. Solid (1·55 g.) was obtained which melted constantly at 128—129° after two recrystallisations from ethanol. 2-4′-*Aminostyrylthiophen* forms slightly yellow prisms (Found: C, 71·7, 71·6; H, 5·6. 5·5; N, 7·2, 7·1; S, 15·9, 15·7. $C_{12}H_{11}NS$ requires C, 71·8; H, 5·5; N, 7·0; S, 15·9%). In hot dilute hydrochloric acid it gave the grey hydrochloride.

When boiled with a small amount of acetic anhydride in acetic acid, it gave the acetyl derivative as greenish-yellow needles, m. p. 222°.

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## 578. *Alicyclic Compounds. Part III.* Ultra-violet Absorption, Acidity, and Ring Fission of* cyclo*Hexane*-1 : 3-*diones.*

By Eric G. Meek, J. H. Turnbull, and Walter Wilson.

Ultra-violet absorption studies of several *cyclo*hexane-1 : 3-diones, in ethanol and over a range of pH in 50% ethanol, confirm the view that the monoenols and the corresponding ions are the only major species involved. From these data, $pK_a$ values are calculated and compared with values obtained electrometrically. The extension of Woodward's empirical rules for the calculation of $\lambda_{max.}$ to various enolised α- and β-diketones is discussed. Bathochromic displacements in the absorption of certain cyclic α-diketones and acyclic β-diketones can be correlated with intramolecular hydrogen bonding. The ring fission of several *cyclo*hexane-1 : 3-diones by alkali has been followed spectroscopically.

Woodward and Blout recognised that 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (dimedone) had the ultra-violet absorption characteristics of a (mono)enolised β-diketone (*J. Amer. Chem. Soc.*, 1943, **65**, 562; cf. Heywood and Kon, *J.*, 1940, 713). *cyclo*Hexane-1 : 3-dione (I) exhibited concentration-dependent absorption in alcohol (Bastron, Davis, and Butz, *J. Org. Chem.*, 1943, **8**, 515), an effect later attributed to reversible ionisation of the acidic enol (Blout, Eager, and Silverman, *J. Amer. Chem. Soc.*, 1946, **68**, 566). However apart from the work of Valyashko and Shcherbak (*J. Gen. Chem. U.S.S.R.*, 1938, **8**, 1629),

Table 1. *Light absorption* (0·001% *solutions in ethanol*).

| | Dione (enol) | | Enol ethyl ether [1] | |
|---|---|---|---|---|
| *cyclo*Hexane-1 : 3-dione : | $\lambda_{max.}$ (mμ) | ε | $\lambda_{max.}$ (mμ) | ε |
| Unsubstituted | 253 | 22,300 | 249 | 18,700 |
| 2-Methyl | 261 | 18,800 | 265 | 20,800 |
| 4- or 6-Methyl [2] | 255 | 12,700 [3] | 249 | 16,100 |
| 5 : 5-Dimethyl | 255 | 17,800 | 250 | 19,200 |
| 2 : 5 : 5-Trimethyl | 264 | 13,600 | 268 | 19,200 |
| 2 : 2 : 5 : 5-Tetramethyl [4] | 207 | 1,100 | — | — |
| | 274 | 240 | — | — |

[1] Part II. [2] Possibly a mixture of the two isomers. [3] The sample contained some α-methylglutaric acid, which is transparent at 255 mμ; hence the low ε value. [4] Concn., 0·01%.

whose data appear to be incomplete and even self-contradictory, the influence of pH on the ultra-violet absorption of *cyclo*hexane-1 : 3-diones has not been studied in detail.

The ultra-violet absorptions of several *cyclo*hexane-1 : 3-diones in absolute ethanol have been measured by us (Table 1). The 2 : 2 : 5 : 5-tetramethyl compound cannot

* Part II, *J.*, 1953, 811.

enolise to a conjugated system, and has the weak absorption expected for two isolated carbonyl groups; the remaining diones exhibit intense absorption, similar to that of the corresponding enol ethers. These results therefore confirm the view that the diones are substantially monoenolic in ethanol.

An extended series of measurements was made on each dione, at different pH's in 50% aqueous ethanol (Table 2); the absorption of the 2 : 2 : 5 : 5-tetramethyl compound was independent of pH, and is not included. Numerous extinction curves were drawn; those for *cyclo*hexane-1 : 3-dione are typical (see Figure). The form of these curves, and particularly the single, sharp, isosbestic point show that only two significant species are involved. These can only be the enol (II) and its ion (III), which predominate in acid and in alkaline solutions respectively. The extinction coefficients at $\lambda_{max.}^{enol}$ and $\lambda_{max.}^{enol\ ion}$ vary greatly with pH changes between 4·5 and 8, but approach limiting values at higher or lower pH; this can be demonstrated graphically in each case. The similarity of the $\lambda$ and $\varepsilon$ values of a given enol seen on comparing Tables 1 and 2 shows that negligible ionisation occurred in

TABLE 2. *Light absorption and* $pK_a$ *in 50% aqueous ethanol.*

| | | $E_{1\ cm.}^{1\%}$ | | $pK_a$ | | |
|---|---|---|---|---|---|---|
| pH | $\lambda_{max.}$ (m$\mu$) | at $\lambda_{max.}^{enol}$ | at $\lambda_{max.}^{enol\ ion}$ | Spectroscopic [1] | Mean | Electrometric [5] |
| | | cyclo*Hexane*-1 : 3-*dione* (8·29 *mg./l.*; I.P.[2] 264 m$\mu$, $E_{1\ cm.}^{1\%}$ 1182) | | | | |
| 1·98 | 255 [3] | 1569 | 182 | | | |
| | | ($\varepsilon$ 1·76 × 10⁴) | | | | |
| 4·60 | 256 | 1552 | 213 | 6·43 | | |
| 5·52 | 260 | 1342 | 661 | 6·05 | | |
| 5·90 | 278 | 1123 | 1001 | 6·05 | | |
| 6·22 | 280 | 966 | 1318 | 6·09 | 6·21 | 5·89 |
| 6·84 | 280 | 749 | 1722 | 6·24 | | |
| 7·27 | 280 | 672 | 1809 | 6·42 | | |
| 7·59 | 280 | 592 | 1984 | 6·13 | | |
| 7·99 | 280 | 565 | 2204 | | | |
| 9·50 | 280 | 538 | 2280 | | | |
| 10·30 | 280 [4] | 528 | 2283 | | | |
| | | | ($\varepsilon$ 2·56 × 10⁴) | | | |
| | | 2-*Methyl*cyclo*hexane*-1 : 3-*dione* (5·05 *mg./l.*; I.P. 274 m$\mu$, $E_{1\ cm.}^{1\%}$ 1010) | | | | |
| 2·27 | 264 [3] | 1512 | 202 | | | |
| | | ($\varepsilon$ 1·905 × 10⁴) | | | | |
| 4·40 | 264 | 1367 | 226 | 6·33 | | |
| 5·60 | 265 | 1218 | 303 | 6·73 | | |
| 6·26 | 265 | 1194 | 586 | 6·79 | | |
| 6·50 | 267 | 1099 | 836 | 6·83 | | |
| 6·68 | 270 | 1006 | 891 | 6·81 | 6·63 | 6·76 |
| 6·84 | 287 | 901 | 1139 | 6·74 | | |
| 7·17 | 290 | 867 | 1420 | 6·80 | | |
| 7·37 | 290 | 717 | 1564 | 6·79 | | |
| 7·64 | 290 | 578 | 1802 | 6·31 | | |
| 7·84 | 290 | 560 | 1956 | 6·19 | | |
| 8·42 | 290 | 541 | 2115 | | | |
| 11·50 | 290 [4] | 541 | 2158 | | | |
| | | | ($\varepsilon$ 2·72 × 10⁴) | | | |
| | | 2 : 5 : 5-*Trimethyl*cyclo*hexane*-1 : 3-*dione* (5·42 *mg./l.*; I.P. 276 m$\mu$, $E_{1\ cm.}^{1\%}$ 748) | | | | |
| 2·0 | 265 [3] | 978 | 125 | | | |
| | | ($\varepsilon$ 1·53 × 10⁴) | | | | |
| 5·19 | 265 | 954 | 148 | 6·98 | | |
| 5·56 | 266 | 928 | 185 | 6·91 | | |
| 6·16 | 267 | 881 | 317 | 7·01 | | |
| 6·25 | 268 | 841 | 377 | 6·90 | | |
| 6·48 | 271 | 701 | 620 | 6·70 | 6·91 | 6·76 |
| 6·97 | 292 | 609 | 891 | 6·88 | | |
| 7·46 | 294 | 465 | 1251 | 6·91 | | |
| 7·97 | 294 | 386 | 1416 | 7·01 | | |
| 9·10 | 294 | 362 | 1550 | | | |
| 12·20 | 295 [4] | 321 | 1550 | | | |
| | | | ($\varepsilon$ 2·42 × 10⁴) | | | |

TABLE 2. (*Continued.*)

| pH | $\lambda_{max.}$ (mμ) | $E^{1\%}_{1\ cm.}$ at $\lambda^{enol}_{max.}$ | $E^{1\%}_{1\ cm.}$ at $\lambda^{enol\ ion}_{max.}$ | $pK_a$ Spectroscopic [1] | $pK_a$ Mean | $pK_a$ Electrometric [5] |
|---|---|---|---|---|---|---|
| **4-*Methyl*cyclo*hexane*-1 : 3-*dione*** (7·43 *mg./l.*; I.P. 265 mμ, $E^{1\%}_{1\ cm.}$ 626) | | | | | | |
| 1·90 | 255 [3] | 827 | 118 | | | |
| | | (ε 1·04 × 10⁴) | | | | |
| 3·94 | 255 | 814 | 124 | | | |
| 5·05 | 255 | 828 | 188 | 6·22 | | |
| 5·31 | 257 | 781 | 232 | 6·23 | | |
| 5·77 | 258 | 713 | 353 | 6·31 | | |
| 6·07 | 260 | 630 | 491 | 6·30 | 6·30 | 6·81 |
| 6·21 | 263 | 602 | 549 | 6·34 | | |
| 6·50 | 279 | 563 | 740 | 6·41 | | |
| 7·00 | 280 | 415 | 922 | 6·29 | | |
| 8·13 | 280 | 312 | 1170 | | | |
| 9·30 | 281 | 276 | 1225 | | | |
| 12·40 | 281 [4] | 320 | 1265 | | | |
| | | | (ε 1·59 × 10⁴) | | | |
| **5 : 5-*Dimethyl*cyclo*hexane*-1 : 3-*dione*** (5·5 *mg./l.*; I.P. 266 mμ, $E^{1\%}_{1\ cm.}$ 973) | | | | | | |
| 3·76 | 257 [3] | 1235 | 181 | | | |
| | | (ε 1·73 × 10⁴) | | | | |
| 4·01 | 258 | 1196 | 245 | 5·40 | | |
| 4·66 | 258 | 1170 | 262 | 5·85 | | |
| 4·86 | 259 | 1162 | 273 | 6·08 | | |
| 5·04 | 259 | 1142 | 318 | 6·06 | | |
| 5·37 | 260 | 1091 | 473 | 6·11 | | |
| 5·67 | 261 | 1036 | 600 | 6·10 | 6·20 | 6·05 |
| 5·75 | 262 | 1011 | 636 | 6·13 | | |
| 5·98 | 262 | 984 | 704 | 6·27 | | |
| 6·22 | 268 | 920 | 882 | 6·29 | | |
| 6·46 | 278 | 813 | 1109 | 6·22 | | |
| 6·74 | 280 | 765 | 1396 | 6·26 | | |
| 7·10 | 282 | 745 | 1654 | 6·46 | | |
| 7·43 | 282 | 582 | 1764 | 6·20 | | |
| 8·40 | 282 | 619 | 1774 | | | |
| 12·50 | 282 [4] | 624 | 1898 | | | |
| | | | (ε 2·66 × 10⁴) | | | |

[1] Let $A_e$ and $B_e$ be $E^{1\%}_{1\ cm.}$ of the pure enol at $\lambda^{enol}_{max.}$ and $\lambda^{enol\ ion}_{max.}$ respectively, and let $A_i$ and $B_i$ be the corresponding values for the enol ion. Then, at a given pH, if $A$ and $B$ are $E^{1\%}_{1\ cm.}$ at $\lambda^{enol}_{max.}$ and $\lambda^{enol\ ion}_{max.}$,

$$pK_e = pH - \log_{10}\left(\frac{B - B_e}{B_i - B_e}\right)\left(\frac{A_i - A_e}{A_i - A}\right)$$

[2] Isosbestic point. [3] $\lambda^{enol}_{max.}$. [4] $\lambda^{enol\ ion}_{max.}$. [5] The dione (*ca.* 0·001 mole) in 50% aqueous ethanol was titrated with 0·1N-sodium hydroxide solution, and the pH measured at intervals. The $pK_a$ value was read in the usual way from the graph of pH against volume of sodium hydroxide added.

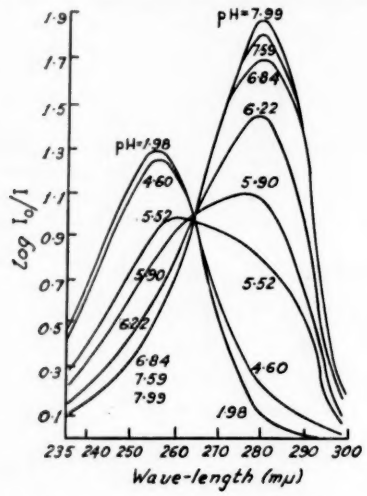
the absolute ethanol. The enol maxima in 50% ethanol are at slightly longer wavelengths than in absolute ethanol; the difference has the magnitude expected (1—2 mμ).

Further considerations confirm the view that monoenols and their ions are the only significant species in solutions of *cyclo*hexane-1 : 3-diones. By an ingenious experimental method, Schwarzenbach and Felder (*Helv. Chim. Acta*, 1944, **27**, 1044) showed that dimedone existed as 95·3% monoenol in water (0·01—0·001M). On theoretical grounds diketo-forms (*e.g.*, I) of *cyclo*hexane-1 : 3-diones should be less stable than their conjugated isomers (II) and (IV); the monoenol (II) is *s-trans* and would therefore be favoured instead of the dienol (IV), which is *s-cis* (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). The α-diketone (V; R = H) has been shown to enolise no further than the monoenol stage, even in strongly alkaline solutions (French and Holden, *J. Amer. Chem. Soc.*, 1945, **67**, 1239).

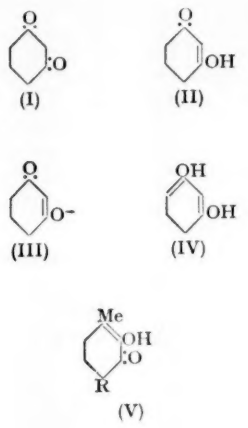
From the results in Table 2, the $pK_a$'s (in 50% alcohol) of the diones have been calculated; values were also determined by an independent electrometric method. The introduction of a 2-methyl substituent notably decreases the acidity of these compounds.

*Extension of Woodward's Rules.*—The following discussion applies to solutions in absolute ethanol. Empirical rules enunciated by Woodward (*J. Amer. Chem. Soc.*, 1941, **63**,

1123; 1942, **64**, 76) permit the calculation of $\lambda_{max.}$ for αβ-unsaturated ketones. *cyclo*-Hexane-1 : 3-dione enols and enol ethers are 3-hydroxy- and 3-ethoxy-*cyclo*hex-2-enones respectively; extending the principles used by Woodward, the bathochromic displacements ($\Delta\lambda_{OH}$ and $\Delta\lambda_{OEt}$) which accompany the introduction of these substituents into the




*Ultra-violet absorption of* cyclo*hexane-1 : 3-dione in 50% ethanol.*




*cyclo*hexenone system, have been calculated (Table 3). A preliminary estimate of $\Delta\lambda_{CH}$ in certain steroids has already been made by Fieser and Fieser (" Natural Products Related to Phenanthrene," Reinhold, New York, 3rd Edn., 1949, p. 195). Comparison of the $\lambda_{max.}$ values of the enols (Table 1) confirms the validity of Woodward's rules in this series, as a

TABLE 3.

| *cyclo*Hexane-1 : 3-dione : | $\Delta\lambda_{OH}$ [1] | $\Delta\lambda_{OEt}$ [2] | *cyclo*Hexane-1 : 3-dione : | $\Delta\lambda_{OH}$ [1] | $\Delta\lambda_{OEt}$ [2] |
|---|---|---|---|---|---|
| Unsubstituted ..... | 28 | 24 | 5 : 5-Dimethyl ..... | 30 | 25 |
| 2-Methyl ..... | 26 | 30 | 2 : 5 : 5-Trimethyl ..... | 29 | 33 |
| 4-Methyl ..... | 30 | 24 | (Mean) ..... | (28·5) | |

[1] $\Delta\lambda_{OH} = \lambda_{max.}^{enol} - \lambda_{max.}^{C}$. [2] $\Delta\lambda_{OEt} = \lambda_{max.}^{enol\ ether} - \lambda_{max.}^{C}$. $\lambda_{max.}^{C}$ refers to the *cyclo*hexenone from which the enols and enol ethers are derived by the introduction of OH or OEt. $\lambda_{max.}$ for *cyclo*hexenone is taken as 225 mμ; this value appears reasonable from data for related compounds (as in Woodward's work, 10 mμ is allowed for a methyl group on the ethylenic centre): 5-*iso*propyl*cyclo*hexenone, $\lambda_{max.}$ 226·5 (Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645); 3-methyl*cyclo*hexenone, $\lambda_{max.}$ 235 (Evans and Gillam, *J.*, 1941, 816); piperitone, $\lambda_{max.}$ 235·5 mμ (Gillam, Lynas-Gray, Penfold, and Simonsen, *J.*, 1941, 60).

2-methyl substituent produces a bathochromic displacement of 8—9 mμ. The $\Delta\lambda_{OH}$ values (Table 3) are reasonably uniform. However, the $\Delta\lambda_{OEt}$ values fall into two groups, 24—25 and 30—33 mμ; the higher value obtained with 2-methyl compounds is possibly a result of steric interaction between the fairly large ethoxy-group and the 2-methyl substituent although steric hindrance is not commonly associated with bathochromic shifts (cf. Braude *et al.*, *loc. cit.*).

It is instructive to compare values of $\lambda_{max.}$ observed for the enols of several acyclic β-diketones and cyclic α-diketones (Table 4) with those computed by using the above value of $\Delta\lambda_{OH}$. It is assumed that the bathochromic shifts resulting from the introduction of α- and β-hydroxyl groups into the system $>C{:}\overset{|}{C}{\cdot}\overset{|}{C}{:}O$ are similar (in the absence of hydrogen bonding). Intramolecular hydrogen-bonding is impossible in *cyclo*hexane-1 : 3-diones (Wheland, " Advanced Organic Chemistry," Wiley, New York, 1949, p. 616), but is possible in all the compounds listed in Table 4. The $\lambda_{max.}$ values observed for these

compounds are usually much higher than those calculated, owing it is believed to intramolecular hydrogen-bonding. The variation in $\Delta\lambda$ seen in Table 4 can be attributed to variations in the extent of intramolecular hydrogen-bonding, especially owing to solvent–solute interaction. Intramolecular hydrogen-bonding is well established for acetylacetone; a similarity between acetylacetone and enolised α-diketones is suggested by the relative $pK_a$ values of acetylacetone, the α-diketone (V; R = H), and *cyclo*hexane-1 : 3-dione (Schwarzenbach *et al.*, *Helv. Chim. Acta*, 1940, **23**, 1147, 1162; 1947, **30**, 663; cf., however, Wheland, *op. cit.*, pp. 611, 616).

Several earlier observations have an important bearing on these general conclusions. Heywood and Kon (*J.*, 1940, 713) referred to unpublished experiments showing that enolised cyclic α- and β-diketones have similar spectra, but the α-maxima are displaced to longer wave-lengths, and Berson (*J. Amer. Chem. Soc.*, 1952, **74**, 5172) has pointed out that derivatives of enolised β-diketones in which hydrogen-bonding is prevented (as in enol ethers or acetates) show a pronounced hypsochromic displacement. The concept of hydrogen-bonding has been used in the interpretation of several other spectra (*e.g.*, by Morton and Stubbs, *J.*, 1940, 1347, and Burawoy and Chamberlain, *J.*, 1952, 3734).

TABLE 4. $\lambda_{max.}$ (mμ) *in ethanol.*

| | Found | Calc.[1] | $\Delta\lambda$ [2] |
|---|---|---|---|
| Diosphenol (V; R = Pr$^i$) | 274 [3] | 263·5 | +10·5 |
| (V; R = H) | 268·5 [4] | 263·5 | + 5 |
| Hydroxymethylenecamphor | 264·5 [3] | 258·5 | + 6 |
| Acetylacetone (enol) | 273 [5] | 253·5 | +19·5 |
| Cholestane-2 : 3-dione, enol (*B*) | 270 [5] | 255·5 | +14·5 |
| ,, ,, enol (*A*) | 272 [6] | 255·5 | +16·5 |
| Cholestane-3 : 4-dione enol | 281 [10] | 272·5 | + 8·5 |
| 3β-Acetoxycholestane-6 : 7-dione enol | 274·5 [7] | 272·5 | + 2 |
| 5-Hydroxyergost-7-ene-3 : 6-dione [9] | 253 [8] | 244 | + 9 |
| 11 : 12-Diketocholanic acid enol | 290 [11] | 272·5 | +17·5 |

[1] Woodward's (1942) constants were used in calculations for the simpler compounds, and Fieser and Fieser's revised constants for steroids (*op. cit.*, p. 192). An increment of 28·5 mμ was added for a hydroxyl group ($\Delta\lambda_{OH}$). [2] $\Delta\lambda = \lambda$ (Found − Calc.). [3] Gillam, Lynas-Gray, Penfold, and Simonsen, *J.*, 1941, 60. [4] French and Holden, *loc. cit.* [5] Blout, Eager, and Silverman, *loc. cit.* [6] Stiller and Rosenheim, *J.*, 1938, 353. [7] Heilbron, Jones, and Spring, *J.*, 1937, 801. [8] Fieser and Fieser (*op. cit.*, p. 181) give $\lambda_{max.}^{CHCl_3}$ 252 mμ; hence $\lambda_{max.}^{EtOH}$ = 253 mμ, by applying the solvent correction factor given by the same authors (p. 184). [9] This compound is neither an α- nor a β-diketone; the 7-en-6-one chromophore, however, could be modified by intramolecular hydrogen-bonding between the 5-hydroxy- and the 6-keto-group. [10] Butenandt *et al.* (*Ber.*, 1936, **69**, 2779) give $\lambda_{max.}^{CHCl_3}$ 280 mμ; hence $\lambda_{max.}^{EtOH}$ = 281 mμ, Fieser and Fieser's solvent correction factor being used. [11] Barnett and Reichstein (*Helv. Chim. Acta*, 1938, **21**, 926) give $\lambda_{max.}^{hexane}$ 279 mμ; hence $\lambda_{max.}^{EtOH}$ = 290 mμ (Fieser and Fieser's solvent correction factor).

*Ring Fission of* cyclo*Hexane*-1 : 3-*diones*.—The well-known formation of γ-acylbutyric acids from *cyclo*hexane-1 : 3-diones by alkali has been studied kinetically by Hinkel, Ayling, Dippy, and Angel (*J.*, 1931, 814). These experiments have now been extended; and a spectroscopic method was used for analysis of dione solutions, being more convenient and probably more reliable than the permanganate titration used by the earlier workers. The velocity constants (Table 5) demonstrate an apparent stabilising effect of a 5 : 5-*gem*-

TABLE 5. *Rates of ring fission at* 100°.

| | $10^5k$ (min.$^{-1}$) | | | $10^5k$ (min.$^{-1}$) | |
|---|---|---|---|---|---|
| *cyclo*Hexane-1 : 3-dione | Hinkel [1] *et al.* | Present work | *cyclo*Hexane-1 : 3-dione | Hinkel [1] *et al.* | Present work |
| Unsubstituted | 95·6 | 133 | 5 : 5-Dimethyl | 6·67 | 5·4 |
| 2-Methyl | — | 136—216 [2] | 2 : 5 : 5-Trimethyl | — | 0 |
| 4-Methyl | — | 132 | | | |

[1] Only those values relevant to the present work are quoted. [2] Not computed graphically; $k$ was calculated at each time interval; mean value, 169. See Experimental section.

dimethyl group on the ring; for example, no detectable hydrolysis occurred with the 2 : 5 : 5-trimethyl dione. It has been reported also that the 4 : 5 : 5-trimethyl dione is not hydrolysed by barium hydroxide solution (Crossley, *J.*, 1901, 138). The stabilities of *cyclo*-

hexane-1 : 3-diones in air and in alkali are not parallel, as the spontaneous decomposition which occurs in air is probably an oxidative ring fission (Part II).

### Experimental

The *cyclo*hexane-1 : 3-diones were freshly purified samples of those described in Part II. Spectroscopic data were measured with a Unicam SP. 500 Spectrophotometer, with 10-mm. cells. The ethanol used was the "commercial absolute" grade. pH's were measured with a Cambridge meter, and calomel and glass electrodes.

*Ring Fission of* 2-*Methyl*cyclo*hexane*-1 : 3-*dione*.—The dione (4·2 g.), water (35 c.c.) and sodium hydroxide (2·6 g.) were heated at 100° for 8 hr. Acidification (pH 3) precipitated the original dione (3·0 g., 72%); ether-extraction of the filtrate afforded 5-ketoheptanoic acid (1·1 g., 26%), b. p. 90—102°/0·01 mm., m. p. 47—49°, $\lambda_{max.}$ 262 mμ (ε 73) (semicarbazone, m. p. 185—186°) (Blaise and Maire, *Bull. Soc. chim.*, 1908, **3**, 421, give m. p. 50° and semicarbazone, m. p. 196°). In a similar experiment with the 2 : 5 : 5-trimethyl dione, no change was detected after 20 hr.' refluxing.

*Kinetic Measurements*.—The diones were hydrolysed in a 100-c.c. 2-necked flask, fitted with an efficient reflux condenser, on a steam-bath, in a slow stream of moist, $CO_2$-free nitrogen, which stirred the mixture; losses by evaporation were negligible. The dione (1 g.) was dissolved in 2N-sodium hydroxide (100 c.c.), and about three-quarters of the solution put in the reaction vessel. At suitable intervals, small portions of liquid were removed and acidified to pH 2—3, suitably diluted with 50% aqueous ethanol, and the ultra-violet extinction at $\lambda_{max.}^{enol}$ measured. First-order rate constants were computed by means of the equation $k = (2{\cdot}303/t) \log_{10} (E_0/E_t)$ where $E_t$ is $E_{1\,cm.}^{1\%}$ (at $\lambda_{max.}^{enol}$) after $t$ min. and $E_0$ is the initial value, at a convenient time soon after the attainment of thermal equilibrium. Plots of $t$ against log $(E_0/E_t)$ were usually linear, and $k$ could be read off. In hydrolyses in which considerable proportions of γ-acylbutyric acids were formed, $E_t$ values were corrected for the (small) absorption of these acids.

2-Methyl*cyclo*hexane-1 : 3-dione gave plots which deviated from linearity, by much more than reasonable experimental error. Similar deviations were observed by Hinkel *et al.* in the hydrolysis of certain other 2-substituted *cyclo*hexane-1 : 3-diones.

The authors are grateful for encouragement by Professor M. Stacey, F.R.S., and thank Mr. W. White for assistance with spectroscopic measurements.

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## 579. *The Reactivity of the* O-*Acylglycosyl Halides. Part I. The Solvolytic Reactions of Tetra*-O-*acetyl*-α-D-*glucopyranosyl* 1-*Bromide.*

By F. H. Newth and G. O. Phillips.

Solvolytic reactions of tetra-*O*-acetyl-α-D-glucopyranosyl 1-bromide have been examined kinetically. The first-order rate constants are greater in the more polar solvents, and in the presence of alkali the rate is unaffected. Racemization has been observed in aqueous-acetone solution. These results show that the nucleophilic substitution is unimolecular.

The series of sugar derivatives which possess a halogen atom at the potential reducing group in the molecule, the *O*-acyl-glycosyl 1-halides, is well established. The halogen is reactive and with nucleophilic reagents substitution occurs readily. Until 1924 it was believed that the stable form of tetra-*O*-acetyl-D-glucosyl 1-bromide (acetobromoglucose) was a β-derivative. The evidence for this classification lay solely in the fact that it yields acetylated β-glucosides or the β-penta-*O*-acetate when the halogen is replaced (Koenigs and Knorr, *Ber.*, 1901, **34**, 95). Hudson, however, revised the classification of the acetyl-halogeno-derivatives of the sugars as α- or β-forms on the basis of their optical rotatory powers (*J. Amer. Chem. Soc.*, 1924, **46**, 462; Phelps and Hudson, *ibid.*, p. 2591) and the common tetra-*O*-acetyl-D-glycosyl 1-bromide and 1-chloride were shown to be α-derivatives. It follows that inversion occurs in the replacement reactions of the halogen atom. The

Koenigs–Knorr reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide leads to the corresponding tetra-*O*-acetyl-β-D-glucoside and in this reaction inversion is complete and the yield almost quantitative.

It has been pointed out by Frush and Isbell (*J. Res. Nat. Bur. Standards*, 1941, **27**, 412) that this is the normal course of the reaction when the acetyl group at $C_{(2)}$ in the sugar molecule is *cis* to the halogen atom. When the halogen atom and the neighbouring acetyl group are *trans* to one another, however, the reaction with methanol in the presence of silver carbonate or quinoline leads to the formation of a methyl 1 : 2-orthoacetate together with the anomeric α- and β-glycosides. In the analogous reaction with water, a tetra-acetate is produced which has the same configuration as the parent halide. Fresh evidence has been adduced recently by Fletcher and Hudson (*J. Amer. Chem. Soc.*, 1950, **72**, 4173) and Ness, Fletcher, and Hudson (*ibid.*, 1951, **73**, 296, 959) who have examined the reactions of the *O*-benzoyl 1-halides of several sugars and confirm the importance of the acyl group at $C_{(2)}$. These authors showed that the halides gave first-order rate constants in methanol–dioxan (9 : 1). Kinetic order is, however, not diagnostic of mechanism and a particular technique is necessary for its determination (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 611).

Although the reaction of the *O*-acylglycosyl 1-halides with alcohols is normally carried out in the presence of an acid acceptor, it is known that complicated kinetic results are obtained in the presence of silver salts. An examination of the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide has been made, therefore, with hydroxylic solvents alone. Two methods were used : one was to follow the change of optical rotation, and the other was to measure the acid liberated during the reaction by titration with standard alkali. The two methods gave good agreement, $10^5k^{21\cdot2}$ being 2·83 and 2·80 (sec.$^{-1}$) respectively in 100% methanol. Koenigs and Knorr (*loc. cit.*) found that deacetylation occurred during the methanolysis when the concentration of tetra-*O*-acetyl-α-D-glucosyl 1-bromide was *ca.* 0·5M, and methyl β-D-glucoside was formed. Ness, Fletcher, and Hudson (*loc. cit.*) also reported partial deacetylation during methanolysis of 1·0M-tri-*O*-acetyl-α-L-rhamnosyl 1-bromide, but deacetylation was not observed with the tri-*O*-benzoate. In the present work, 0·02—0·06M-solutions have been used and deacetylation by liberated hydrogen ions was only detected when the reaction was slow and at an elevated temperature. The titrimetric method had the advantage that the amount of alkali required to neutralise the liberated acid could be calculated and compared with the final, experimental value. In the polarimetric experiments, occurrence of deacetylation could be inferred only from the final value of the optical rotation.

Catalysis by liberated hydrobromic acid was observed and Fig. 1 shows that this was negligible during the first 70% (240 min.) of the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in 100% methanol but becomes significant at higher concentrations of hydrogen bromide. Thus after 160 min. it is just evident when the initial concentration of added hydrogen bromide is 0·003M and marked when it is 0·023M. The initial values of $10^5k^{21\cdot2}$ were 2·80, 2·81, and 4·48 (sec.$^{-1}$) respectively in simultaneous runs. A similar behaviour observed with unimolecular reactions and called the " salt effect " (Bateman, Hughes, and Ingold, *J.*, 1940, 960; Bell, " Acid–Base Catalysis," Oxford Univ. Press, 1941, p. 11) is attributed to the accumulation of ions in the reaction medium as the reaction proceeds, which increases the ionizing properties of the medium and facilitates the ionization of the C–Hal bond. A mass-law influence is also believed to be superimposed on this by the anions produced but this would be negligible compared with the effect of the increase in ionic strength. In the presence of a neutral bromide a slight increase in rate was observed. Simultaneous polarimetric measurements gave values of 2·03 (sec.$^{-1}$) in methanol alone and 2·14 (sec.$^{-1}$) in methanol containing 0·04M-lithium bromide for $10^5k^{18}$. With tetra-*O*-acetyl-α-D-glucosyl 1-bromide and other *O*-acetylglycosyl 1-halides studied later the effect of acceleration by liberated acid has been avoided by considering only the first 50% of the reaction for rate-measurement purposes.

The effect of the addition of various concentrations of sodium hydroxide on the rate of reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in 60% aqueous acetone is summarised in Table 1. The rate is obviously independent of the concentration of hydroxyl ions. Since such a powerful nucleophilic reagent does not alter the rate of reaction at all, it

indicates strongly that the solvent does not take part in the rate-determining stage. The possibility of a bimolecular mechanism occurring in the 60% aqueous acetone is thus eliminated. (Aqueous acetone was chosen as the medium in which to investigate the effect of alkali on the reaction because deacetylation by the hydroxyl ion is very slow. In absolute alcoholic alkali, deacetylation would have been an important side reaction.)

TABLE 1. *Rate of reaction of tetra-*O*-acetyl-α-*D*-glucosyl 1-bromide in* 60% *aqueous acetone in the presence of sodium hydroxide.* [Halide] ≈ 0·05M.

| [NaOH] (N) | — | 0·025 | 0·075 |
|---|---|---|---|
| $10^5k^{21\cdot2}$ (sec.$^{-1}$) | 5·09 | 5·03 | 5·03 |

The effect of solvent changes on the reaction rate gives auxiliary evidence of reaction mechanism (Hughes, *loc. cit.*). In a more ionizing solvent, both $S_N1$ and $S_N2$ mechanisms should be facilitated, but the $S_N1$ mechanism is affected more strongly by

FIG. 1.

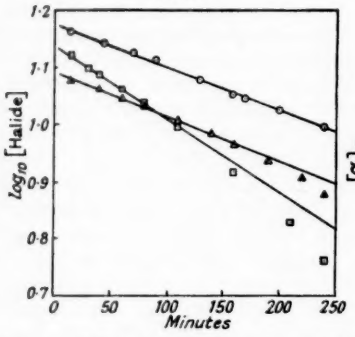


FIG. 2.

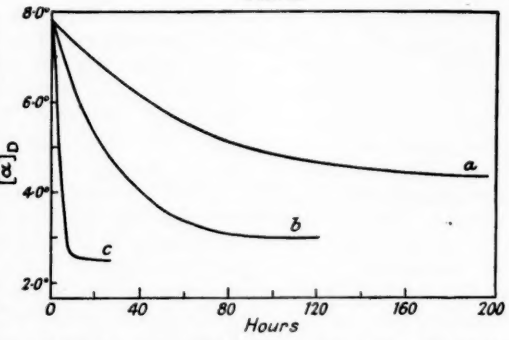


FIG. 1. *Effect of acid on the reaction of tetra-*O*-acetyl-α-*D*-glucosyl 1-bromide with methanol at* 21·2°.
○ *Methanol alone.* △ *Methanol initially* 0·003N *with respect to* HBr.
□ *Methanol initially* 0·023N *with respect to* HBr.

FIG. 2. *Effect of aqueous-acetone media on the hydrolysis of tetra-*O*-acetyl-α-*D*-glucosyl 1-bromide.*
(*a*) 87·6%, (*b*) 76·9%, (*c*) 60% *Aqueous acetone* ($c = 1$; $l = 4$).

solvation factors. In Table 2 are shown the first-order rate constants for the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide with hydroxylic media. It can be seen that the rate increases when the amount of water in aqueous methanol is increased. Similarly the rate increases with the amount of water in aqueous acetone and is decreased by addition of acetone to methanol. The observed increase in rate is less than that which has been determined for the unimolecular solvolysis of *neo*pentyl or *iso*propyl bromide (Dostrovsky,

TABLE 2. *The effect of solvent variation on the rate of solvolysis of tetra-*O*-acetyl-α-*D*-glucosyl 1-bromide at* 21·2°. [Halide] = 0·05M.

| Medium | $10^5k$ (sec.$^{-1}$) | Medium | $10^5k$ (sec.$^{-1}$) |
|---|---|---|---|
| 100% Methanol | 2·80 | 90% Aq. acetone | 0·14 |
| ,, ,, | 2·83 * | 80% ,, | 0·50 |
| 90% Aq. methanol | 5·80 | 70% ,, | 1·78 |
| 87·4% ,, | 6·33 * | 60% ,, | 4·89 |
| 80% ,, | 11·12 | 90% Methanol–acetone | 1·19 |
| 70% ,, | 22·7 | 70% ,, | 0·82 |
| 60% ,, | 36·1 * | 50% ,, | 0·35 |

* Polarimetric method.

Hughes, and Ingold, *J.*, 1946, 173), but comparison of a cyclic with an acyclic halide is not strictly valid.

Bimolecular substitution at an asymmetric carbon atom invariably leads to inversion, whereas a unimolecular mechanism permits either retention or inversion. The hydrolysis

of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in aqueous acetone was examined polarimetrically and Fig. 2 shows the rate of change of rotation in 60%, 76·9%, and 87·6% aqueous acetone. As the ionizing power of the medium increases the rate shows a marked increase (values for $k$ in similar media are given in Table 2), and the final value of the rotation depends upon the medium. Tetra-*O*-acetyl-D-glucose is the sole product of the reaction, and a higher final value for $\alpha_D$ in the medium containing the more inert solvent must represent an increase in the amount of the (+)-α-form in the product. This racemization can only be explained if the unimolecular mechanism is operating. This conclusion was supported by a qualitative examination of the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide with sodium iodide in acetone. The reaction at 20° was too fast to measure, and after 10 min. tetra-*O*-acetyl-α-D-glucosyl 1-iodide was isolated in 76% yield. The significant feature, in addition to the velocity, is the almost complete retention of configuration under conditions which are most conducive to operation of the bimolecular mechanism.

## Experimental

*Purification of Solvents.—Methanol.* Acetone and formaldehyde were detected by the method of Hartley and Raikes (*J.*, 1925, **127**, 524) and were removed by the hypoiodite method of Bates, Mullaly, and Hartley (*J.*, 1923, **123**, 401). After boiling with calcium oxide the methanol was dried over magnesium and fractionally distilled through a Fenske-packed column. The fraction, $n_D^{20}$ 1·3288, boiling at 64·7°/760 mm. was collected. The water content was less than 0·02% (Karl Fischer).

*Acetone.* "AnalaR" solvent was dried over calcium chloride and distilled. The fraction boiling at 56°/760 mm. was collected.

The term $x$% aqueous methanol or aqueous acetone used in this work refers to a medium obtained by mixing at room temperature $x$ volumes of dry solvent with $(100 - x)$ volumes of distilled water. Similarly, $x$% methanol–acetone refers to a mixture of $x$ volumes of methanol with $(100 - x)$ volumes of acetone.

*Tetra-O-acetyl-α-D-glucosyl 1-Bromide.*—This was prepared from either α- or β-penta-*O*-acetylglucose by treatment with hydrogen bromide in glacial acetic acid. The crystalline product was recrystallised from dry ether until the m. p. was 88—89°.

*Rate Measurements.*—(a) *Titrimetric method.* In each experiment a weighed quantity of the halide was dissolved in the required medium in a 50-ml. standard flask to give an approx. 0·05M-solution. Both halide and solvent were kept at the temperature of the thermostat (21·2° ± 0·05°) before mixing. Zero time was taken when half the solvent had been added. At known intervals 5-ml. aliquots were withdrawn and run into 50 ml. of absolute ethanol which had been cooled in acetone–carbon dioxide. The solution was titrated with standard alcoholic potassium hydroxide (*ca.* 0·02N), with lacmoid as indicator. The initial concentration of halide was given by the titre at infinite time. $\text{Log}_{10}$ [Halide] was plotted against time, $t$, and the first-order rate constant given by $k = -2{\cdot}303 \times$ slope of line (sec.$^{-1}$). The rate constants are listed in Table 2, and some individual runs are illustrated below :

Concentrations of halide are expressed in equivalent ml. of standard alkali per 5 ml. of solution. $k$ is in sec.$^{-1}$.

90% *Aqueous methanol.*

| $t$ (min.) ..... | 0 | 30 | 45 | 60 | 75 | 105 | 120 | 150 | 180 | 225 | 250 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] ..... | 8·09 | 7·26 | 6·89 | 6·56 | 6·20 | 5·59 | 5·30 | 4·79 | 4·32 | 3·72 | 3·39 |

[Halide] = 0·0486M by wt. [KOH] = 0·030N.
Slope of line : $-1{\cdot}51 \times 10^{-3}$ min.$^{-1}$. $10^5k = 5{\cdot}80$.

70% *Methanol–acetone.*

| $t$ (min.) ..... | 0 | 20 | 40 | 60 | 90 | 120 | 150 | 200 | 250 | 300 |
|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] ..... | 9·78 | 9·68 | 9·57 | 9·46 | 9·37 | 9·18 | 9·02 | 8·78 | 8·53 | 8·32 |

[Halide] = 0·0491M by wt. [KOH] = 0·0251N.
Slope of line : $-2{\cdot}084 \times 10^{-4}$ min.$^{-1}$. $10^5k = 0{\cdot}82$.

70% *Aqueous acetone.*

| $t$ (hr.) ..... | 0 | 1 | 2 | 3 | 5 | 6 | 8·5 | 10 |
|---|---|---|---|---|---|---|---|---|
| [Halide] ..... | 8·71 | 8·19 | 7·63 | 7·19 | 6·31 | 5·92 | 5·04 | 4·58 |

[Halide] = 0·0487M by wt. [KOH] = 0·0270N.
Slope of line : $-2{\cdot}786 \times 10^{-2}$ hr.$^{-1}$. $10^5k = 1{\cdot}78$.

(b) *Polarimetric method.* A known amount of the halide was dissolved in the appropriate medium ($c \sim 1$) and put into a polarimeter tube (2 or 4 dm.). The first-order rate constant was calculated from the slope of the line obtained by plotting $\log_{10}(\alpha_t - \alpha_\infty)$ against time where $\alpha_t$ is the optical rotation at time, $t$, and $\alpha_\infty$ that at infinite time. The rate constants are listed in Tables 1 and 2 and an individual run is illustrated below.

100% *Methanol.* 21·2°.

| $t$ (min.) ... | 10 | 25 | 50 | 85 | 100 | 120 | 135 | 150 | 175 | 200 | 225 | 300 | ∞ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\alpha_D$ ..... | 8·34° | 8·16° | 7·82° | 7·45° | 7·09° | 6·97° | 6·79° | 6·60° | 6·36° | 6·10° | 5·84° | 4·92° | −02·1 |

$c$, 2·165; $l$, 2. Slope: $-7{\cdot}37 \times 10^{-4}$ min.$^{-1}$. $10^5k = 2{\cdot}83$ (sec.$^{-1}$).

*Reaction of Tetra-O-acetyl-α-D-glucosyl 1-Bromide with Sodium Iodide in Acetone.*—The bromide (5 g.) was dissolved in dry acetone (20 ml.) and a solution of sodium iodide (2·5 g.) in acetone (20 ml.) rapidly added at room temperature (20°) with shaking (cf. Helferich and Gootz, *Ber.*, 1929, **62**, 2791). After 10 min. the reaction was stopped by adding water and tetra-*O*-acetyl-α-D-glucosyl 1-iodide (5·34 g.) was isolated, having m. p. 108—109° (Helferich and Gootz give m. p. 109—110°).

The authors thank Professor S. Peat, F.R.S., for his interest in the work described in this and the following two papers, and the Department of Scientific and Industrial Research for a maintenance grant (to G. O. P.).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, March 27th*, 1953.]

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## 580. *The Reactivity of the O-Acylglycosyl Halides. Part II.* The Effect of the Lactol Ring Oxygen Atom.*

By F. H. NEWTH and G. O. PHILLIPS.

The reactivity of the halogen in the *O*-acylglycosyl 1-halides is due to its being part of an α-halogeno-ether system. A comparison with 2 : 3-dichlorotetrahydropyran has been made, and further comparison with 2 : 3-dichlorothia*cyclo*hexane establishes that the hetero-atom is responsible for the ease of unimolecular solvolysis of the $C_{(1)}$–Hal bond. When the halogen is elsewhere in the molecule ($C_{(2)}$ or $C_{(3)}$), solvolysis cannot be detected. The first-order solvolysis of *cyclo*hexyl bromide has been examined.

IT has been pointed out that the high reactivity of the halogen atom in the *O*-acylglycosyl 1-halides is typical of that displayed by α-halogeno-ethers (Pigman and Goepp, "Chemistry of the Carbohydrates," Academic Press Inc., N.Y., 1948, p. 160; Hurd and Holysz, *J. Amer. Chem. Soc.*, 1950, **72**, 2005). The exceptional reactivity of the chloromethyl ethers was discussed by Cocker, Lapworth, and Walton (*J.*, 1930, 440), and Hughes and Ingold (*J.*, 1935, 244) predicted that the reactions of such compounds would belong to the $S_N1$ class. The inductive polarization of the C–Cl bond will be increased by an electromeric release of electrons from the oxygen atom, and the effect of electron accession to the centre of reaction in a nucleophilic substitution is to promote a unimolecular rather than a bimolecular mechanism. In Part I* it was shown that solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide is unimolecular. The present work is concerned with an assessment, by a quantitative examination of analogous compounds, of the extent to which the lactol ring oxygen atom promotes C–Hal bond fission.

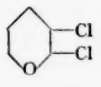
An unsuccessful attempt was made by Clarke (*J.*, 1910, 417) to follow the reaction of chloromethyl methyl ether with alcoholic pyridine, but Conant, Kirner, and Hussey (*J. Amer. Chem. Soc.*, 1925, **47**, 497) were able to measure the rate of reaction with sodium iodide in acetone. Acid catalysis was found (Böhme, *Ber.*, 1941, **74**, 248), and Leimu and Salomaa (*Acta Chem. Scand.*, 1947, **1**, 353), who examined the solvolysis of the 1-chloromethyl ethers, noticed acid catalysis in the apparently unimolecular reaction.

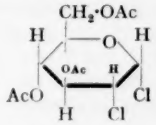
Although it is considered that the same electron transfers operate in the *O*-acylglycosyl

* Part I, preceding paper.

1-halides as in the 1-chloroalkyl ethers, comparison between cyclic and acyclic structures is not entirely satisfactory. For this reason, a 2-halogenotetrahydropyran was examined. The reactions of 2 : 3-dihydro-4*H*-pyran with halogens and hydrogen halides have been well studied (Jones and Taylor, *Quart. Reviews*, 1950, **4**, 195) : the dihalides undergo alcoholysis and dehydrohalogenation very readily, to give the 2-alkoxy-3-halogenotetrahydropyran and 5 : 6-dihydro-3-halogeno-4*H*-pyran respectively. The 2-halides, although too unstable to be isolated (Paul, *Compt. rend.*, 1944, **218**, 122), give the 2-alkoxy-derivatives.

2 : 3-Dichlorotetrahydropyran (I), obtained by chlorination of dihydropyran, decomposed when kept, and even when freshly prepared contained hydrogen chloride. The methanolysis of a freshly prepared sample followed the first-order rate law and was not catalysed by the liberated acid. The rate-constant is compared in Table 1 with that for the methanolysis of 3 : 4 : 6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucosyl 1-chloride * (II) and has a value more than 800—1000 times as great as that for the glucose derivative (II) and tetra-*O*-acetyl-α-glucosyl 1-bromide. The product from methanolysis of 2 : 3-dichlorotetrahydropyran contained, in addition to 3-chlorotetrahydro-2-methoxypyran, 3-chloro-5 : 6-dihydro-4*H*-pyran (11·4%), showing that elimination and substitution were occurring simultaneously. Hydrolysis of the dichloride in 80% aqueous acetone is also very rapid, $10^5k^{21\cdot2}$ being 177 (sec.$^{-1}$) compared with 0·50 (sec.$^{-1}$) for tetra-*O*-acetyl-α-D-glucosyl 1-bromide in the same medium, and the product was 3-chlorotetrahydro-2-hydroxypyran. The unimolecular character of the solvolytic reactions of tetra-*O*-acetyl-α-D-glucosyl 1-bromide has been established (Part I) and it may be inferred that the corresponding reactions in the tetrahydropyran series are also unimolecular. In *trans*-(I) and *cis*-(II), there may be a small Winstein effect but this would be insufficient to explain such a large

(I) 



(II)

difference in rate between the tetrahydropyran and the sugar derivative where the oxygen atom facilitates reaction at the α-carbon atom. The much greater reactivity of the former must be attributed to the absence of large substituent groups in the molecule which can impede reaction at the α-carbon atom in the latter. Such steric effects are discussed more fully in the following paper.

It is well known that the electromeric effect of sulphur is less than that of oxygen and, consequently, the reactivity of a 2-halogenothia*cyclo*hexane would be expected to be less

TABLE I.

*Comparison of the rate of methanolysis of* 2 : 3-*dichlorotetrahydropyran with that of several* O-*acetylglycosyl* 1-*halides.*

| Compound | $10^5k$ (sec.$^{-1}$) | Temp. |
|---|---|---|
| 2 : 3-Dichlorotetrahydropyran | 644 | 21·2° |
| Tetra-*O*-acetyl-α-D-glucosyl 1-bromide | 2·8 | 21·2 |
| Tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucosyl 1-chloride | 0·96 | 35 |
| Tetra-*O*-acetyl-α-D-glucosyl 1-chloride | 0·42 | 35 |

than that of the analogous tetrahydropyran. In the acyclic series, Böhme (*Ber.*, 1941, **74**, 248) compared the reactivities of alkyl 1-chloromethyl ethers and sulphides and found the first-order solvolysis of the sulphides to be much slower. In the present work, thia*cyclo*hex-2-ene (III), prepared according to Naylor (*J.*, 1949, 2749), gave 2 : 3-dichlorothia*cyclo*hexane (IV) by addition of chlorine. This dichloro-derivative was a distillable liquid which did not decompose with such rapidity as the tetrahydropyran derivative. In its reaction with methanol at 21·2°, the first-order constant decreased during the reaction, in a manner

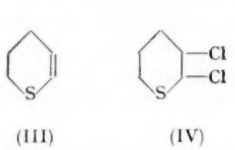
* The dichlorotetrahydropyran presumably has *trans*-halogen atoms, by normal double-bond addition, whereas in the 1 : 2-dichloroglucose it can be deduced that they are *cis*. The glucose configuration is present since treatment with ammonia gives *epi*glucosamine (3-amino-3-deoxyaltrose) which could not arise from a 2-chloro-2-deoxymannose derivative. The 1-halogen atom has the α-configuration since with methanol a β-glycoside is formed (Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509).

similar to, but more pronounced than, that observed by Böhme with the acyclic compounds (*loc. cit.*). A comparison with 2 : 3-dichlorotetrahydropyran is shown in Table 2, where it is seen that the reaction of the sulphur compound is much slower. This establishes that, in these compounds, the hetero-atom is largely responsible for the ease of nucleophilic displacement of the halogen by virtue of its ability to release electrons to the seat of substitution. Further support for this is found in the inertness of the halogen atom when it is not part of the α-halogeno-ether system. Such sugar halides are much more resistant to solvolysis. Methyl 2-chloro-2-deoxy-β-D-glucoside (V), its 3 : 4 : 6-triacetate, and methyl 3-chloro-3-deoxy-α-D-glucoside (VI) were each heated with methanol at 98° for 500 hr.: in no instance was any reaction detected and the compounds were recovered unchanged. It should be remembered that although this type of compound resists alcoholysis, the formation of an anhydro-ring occurs easily with alkaline reagents.

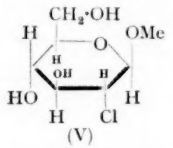
TABLE 2. *Methanolysis of* 2 : 3-*Dichlorotetrahydropyran* (I) *and* 2 : 3-*Dichlorothiacyclohexane* (IV) at 21·2°. [Halide] = 0·05M.

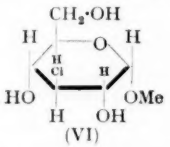
| *t* (min.) | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 20 | 35 | 45 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reaction, %; (I) | 37·5 | 56·6 | 70·6 | 79·6 | 86·9 | 95·5 | — | — | — | — | — |
| Reaction, %; (IV) | 14·9 | — | — | 25·3 | — | 30·1 | 37·5 | 42·9 | 52·0 | 57·4 | 66·0 |

In the foregoing discussion, the influence of the lactol oxygen atom in the *O*-acylglycosyl 1-halides has been examined and it has been suggested that the substituent acyloxy-groups play an important part in the solvolytic reactions of these compounds. At this point it is convenient to make a comparison with *cyclo*hexyl bromide. This molecule contains only the six-membered alicyclic ring and the secondary halogen atom, and the absence of the lactol oxygen atom and acyloxy-groups would be expected to have a considerable effect on reactivity. The solvolysis of *cyclo*hexyl bromide at 95° in aqueous ethanol gave values of $10^5k$ of 3·58 ± 0·02 (sec.$^{-1}$) and 16·6 ± 0·3 (sec.$^{-1}$) in 70% and 50% aqueous ethanol respectively [cf. $10^5k^{21\cdot2} = 22\cdot7$ (sec.$^{-1}$) in 70% aqueous methanol for tetra-*O*-acetyl-α-D-glucosyl 1-bromide]. The ratio $k^{50\%}/k^{70\%}$ is of the same order as that for *iso*propyl bromide


(III)


(IV)


(V)


(VI)

in its unimolecular reaction (Hughes, Ingold, and Shapiro, *J.*, 1936, 225). The solvolysis of *cyclo*hexyl bromide was accompanied by almost complete elimination (95%), as would be expected if the bromine were polar in its attachment to the ring (Barton, *J.*, 1953, 1027). In view of this, comparison with the *O*-acylglycosyl 1-halides must be carried no further than to point out that the *cyclo*hexyl derivative is much less reactive than molecules containing the lactol ring.

## EXPERIMENTAL

*Solvents.*—Methanol and acetone were purified as described in the previous paper. Ethanol was purified by Manske's method (*J. Amer. Chem. Soc.*, 1931, **53**, 1106). The term *x*% aqueous alcohol or aqueous acetone has the same significance as in Part I.

2 : 3-*Dichlorotetrahydropyran.*—Dry chlorine was passed into an ice-cold solution of dihydropyran (50 g.; b. p. 84—86°, $n_D^{20}$ 1·4400) in carbon tetrachloride (100 ml.) until 42 g. had been absorbed. The colourless solution had an acid reaction and, after removal of solvent and excess of dihydropyran under reduced pressure, the residual liquid was distilled. The fraction boiling at 80—83°/20 mm., $n_D^{20}$ 1·4937 (30 g.), was collected (cf. b. p. 74°/11 mm., $n_D^{25}$ 1·495, given in B.P. 571,265). The 2 : 3-dichlorotetrahydropyran obtained in this way contained too much acid for kinetic measurements and it was more satisfactory to use the product immediately after passage of slightly less than the theoretical amount of chlorine and removal of the solvent (Found: Cl, 45·4. Calc. for $C_5H_8OCl_2$: Cl, 45·8%).

*Thia*cyclo*hex*-2-*ene.*—This was prepared according to Naylor (*loc. cit.*) by passing dihydropyran and hydrogen sulphide over alumina at 400°. The product had b. p. 142—144°, $n_D^{20}$ 1·5348 (Naylor gives b. p. 142—145°, $n_D^{20}$ 1·5330).

2 : 3-*Dichlorothia*cyclo*hexane*.—Thia*cyclo*hex-2-ene (5 g.) in carbon tetrachloride (100 ml.) was treated with dry chlorine (3·2 g., 90%) at 0°. The solvent was removed and the 2 : 3-*dichlorothia*cyclo*hexane* distilled at 100—106°/20 mm., $n_D^{17}$ 1·5593 (6·5 g.) (Found : C, 35·1; H, 4·7; S, 18·5. $C_5H_8Cl_2S$ requires C, 35·0; H, 4·7; S, 18·7%).

*Tetra*-O-*acetyl*-α-D-*glucosyl* 1-*Chloride*.—This was obtained from penta-*O*-acetyl-β-D-glucose by the action of titanium tetrachloride in chloroform (Brauns, *J. Amer. Chem. Soc.*, 1925, **47**, 1280). It had m. p. 75—76°, $[\alpha]_D^{20}$ +166° (*c*, 2·0 in $CHCl_3$).

3 : 4 : 6-*Tri*-O-*acetyl*-2-*chloro*-2-*deoxy*-α-D-*glucosyl* 1-*Chloride*.—This was prepared by adding chlorine to tri-*O*-acetyl-D-glucal (Fischer, Bergmann, and Schotte, *loc. cit.*). It had m. p. 91—92°, $[\alpha]_D^{20}$ +170° (*c*, 1·5 in $CHCl_3$).

*Methyl* 3 : 4 : 6-*Tri*-O-*acetyl*-2-*chloro*-2-*deoxy*-β-D-*glucoside*.—This, m. p. 148°, was formed when the above compound reacted with methanol in the presence of silver carbonate. Deacetylation of the triacetate with methanolic ammonia provided methyl 2-chloro-2-deoxy-β-D-glucoside, m. p. 159—160° (Fischer, Bergmann, and Schotte, *loc. cit.*).

*Methyl* 3-*Chloro*-3-*deoxy*-α-D-*glucoside*.—Separated from the products of the reaction of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside with hydrochloric acid, this had m. p. 136—138° (Newth, Overend, and Wiggins, *J.*, 1947, 10).

*Methanolysis of* 2 : 3-*Dichlorotetrahydropyran*.—The compound (15 g.) was dissolved in dry methanol (100 ml.) and kept at 35° for 48 hr. Acid was neutralised ($Ag_2CO_3$) and, after removal and washing of the inorganic precipitate, the methanol was removed. 3-Chlorotetrahydro-2-methoxypyran (11·3 g.) had b. p. 85°/750 mm., $n_D^{19}$ 1·4580 (cf. b. p. 38°/2 mm., $n_D^{20}$ 1·4576, given in B.P. 598,080). 3-Chloro-2 : 3-dihydro-4*H*-pyran (1·3 g.) was also obtained boiling at 141—142°, with $n_D^{19}$ 1·4808 (cf. b. p. 141—142°, $n_D^{25}$ 1·479, given in B.P. 571,265).

*Solvolysis of* 2 : 3-*Dichlorotetrahydropyran in* 80% *Aqueous Acetone*.—The compound (5 g.) was dissolved in 80% aqueous acetone (100 ml.) and kept at 20° for 56 hr. The solution was extracted with ether, and the extract washed with dilute sodium hydrogen carbonate solution and water. After drying ($Na_2SO_4$), the ether was evaporated. 3-Chlorotetrahydro-2-hydroxypyran, recrystallised from alcohol, had m. p. 62° (Found : Cl, 27·0. Calc. for $C_5H_9O_2Cl$ : Cl, 25·8%).

*Rate Measurements*.—The course of a reaction was followed by titrating the acid liberated with standard alkali as described in Part I. $Log_{10}$ [Halide] was plotted against time, *t*, and the first-order rate constant given by $k = -2{\cdot}303 \times$ slope of line (sec.$^{-1}$). The following run is typical. Concentrations of halide are expressed in equivalent ml. of standard alkali per 5 ml. of solution.

*Methanolysis of tri*-O-*acetyl*-2-*chloro*-2-*deoxy*-α-D-*glucosyl* 1-*chloride at* 35°.

| *t* (min.) | 0 | 20 | 40 | 60 | 100 | 140 | 180 | 220 | 260 |
|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 9·51 | 9·39 | 9·29 | 9·18 | 8·97 | 8·77 | 8·57 | 8·37 | 8·18 |

[Halide] = 0·019M by wt. Alkali = 0·01N.
Slope : $-2{\cdot}5 \times 10^{-4}$ min.$^{-1}$. $k = 0{\cdot}96 \times 10^{-5}$ sec.$^{-1}$.

cyclo*Hexyl Bromide*.—The thermostat was adjusted to 95·1° ± 0·05°. *cyclo*Hexyl bromide was dissolved in the appropriate medium and 10-ml. aliquots were placed in a series of tubes. These were filled with nitrogen before sealing and immersed in the thermostat for given lengths of time. On removal, a tube was cooled in ice, cleaned, and broken under water (50 ml.). The liberated acid was titrated with standard alkali. The first-order rate constant was calculated from $k = (2{\cdot}303/t) \log_{10}$ [Halide]. The details of the solvolysis of *cyclo*hexyl bromide in 50% aqueous acetone are given below. Concentrations of halide are expressed in equivalent ml. of standard alkali per 10 ml. of solution.

| *t* (min.) | 0 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 25·92 | 21·56 | 19·51 | 17·43 | 15·77 | 14·27 | 12·89 | 11·51 | 10·64 | 9·02 |
| $10^4k$ (sec.$^{-1}$) | — | 1·54 | 1·58 | 1·65 | 1·66 | 1·66 | 1·66 | 1·69 | 1·73 | 1·76 |

Each tube contained 0·0423 g. of $C_6H_{11}Br$. Alkali = 0·010N. Mean $k = 1{\cdot}66 \pm 0{\cdot}03 \times 10^{-4}$ sec.$^{-1}$.

*Treatment of Methyl Chlorodeoxy*-D-*glucosides with Methanol at* 98°.—Methanol solutions (0·05M) of methyl 3 : 4 : 6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucoside, methyl 2-chloro-2-deoxy-β-D-glucoside, and methyl 3-chloro-3-deoxy-α-D-glucoside were heated at 98° in sealed tubes for 500 hr. No acidity developed and each compound was recovered quantitatively.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, March 27th*, 1953.]

## 581. *The Reactivity of the O-Acylglycosyl Halides. Part III.* Steric Effects.*

By F. H. Newth and G. O. Phillips.

The reactivity of *O*-acylglycosyl 1-halides has been related to structure by a kinetic examination of selected compounds, all of which undergo unimolecular solvolysis. The difference between the methanolysis rate of 3 : 4 : 6-tri-*O*-acetyl-2-trichloroacetyl-β-D-glucosyl 1-chloride and 3 : 4 : 6-tri-*O*-acetyl-β-D-glucosyl 1-chloride is attributed to the steric effect of the 2-trichloroacetyl group. The effect of the acetyl group at positions 2 and 4, and the 6-acetoxymethyl group in tetra-*O*-acetyl-α-D-glucosyl 1-bromide has been assessed by examining the α-acetobromo-derivatives of mannose, galactose, and xylose. The methanolysis rate is directly proportional to the amount of " crowding " about $C_{(1)}$ as shown by accurate scale models.

It was shown in Part I (*J.*, 1953, 2896) that the solvolytic reactions of tetra-*O*-acetyl-α-D-glucosyl 1-bromide operate through the $S_N1$ mechanism, and in this paper several other *O*-acetylglycosyl 1-halides are shown to behave similarly. In the reactions of these compounds, the $S_N1$ mechanism is followed in preference to any other because of the strong electron-releasing capacity of the lactol ring oxygen atom (Part II). In $S_N2$ reactions the effects of steric factors have been evaluated by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173). Steric hindrance in the transition states of these reactions is unfavourable to the bimolecular reaction; it is very pronounced in the *neo*pentyl system where compressions of the order of 1·0 Å were observed. For unimolecular reactions, the effects of steric factors on reaction rates are not nearly so definite. According to Hughes and Ingold (Hughes, *Quart. Reviews*, 1951, **5**, 245) steric factors seem to have no marked effect on the unimolecular solvolysis rates of tertiary halides. Baddeley and Chadwick (*J.*, 1951, 368), however, have shown that the ionisation of an aralkyl halide is subject to steric hindrance, but, in the compounds they studied, pure steric effects were difficult to recognise because of superimposed polar effects. With cyclic structures also there is evidence to indicate that steric factors effect unimolecular solvolysis. Winstein and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 812) examined the acetolysis of *cis*- and *trans*-2-acetoxy*cyclo*hexyl toluene-*p*-sulphonates in which the rate-determining stage is the initial ionisation of the sulphonic ester, and found that the rate of acetolysis of the *trans*- is much greater than that of the *cis*-ester.

By varying the size and position of the groups in the *O*-acylglycosyl 1-halides, effects have been observed which can be attributed directly to steric factors without the danger of ambiguity due to superimposed polar factors. Such a structural investigation was carried out with two aims. First, to obtain quantitative information about the relative reactivity of the *O*-acylhexosyl 1-halides and, secondly, to observe the steric characteristics of the $S_N1$ mechanism. The importance of these steric factors in the reactivity of the *O*-acylglycosyl 1-halides was demonstrated by a comparison of 3 : 4 : 6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl 1-chloride (I) and 3 : 4 : 6-tri-*O*-acetyl-β-D-glucosyl 1-chloride (II). Provided that both compounds react by the same mechanism, the difference in solvolysis rate can be due mainly to the decrease in steric hindrance at $C_{(1)}$ in the latter compound caused by the absence of the bulky trichloroacetyl group at $C_{(2)}$. The polar effect of the trichloroacetyl group would be damped considerably on passing through the saturated carbon atom $C_{(2)}$. The chloride (I) was first prepared by Brigl (*Z. physiol. Chem.*, 1921, **116**, 1) by the interaction of penta-*O*-acetyl glucose and phosphorus pentachloride, and Brigl found that selective hydrolysis of the trichloroacetyl group occurred with ammonia, to give (II). The reactions of both compounds with methanol were of the first order and, in the range investigated, no acid catalysis was observed. The rate constants obtained in various media are summarised in Table 1, and there was the same type of variation as with tetra-*O*-acetylglucosyl 1-bromide when the polarity of the medium

* Part II, preceding paper.

was altered. Furthermore, the rate of solvolysis of each compound in 60% aqueous acetone was unaltered by adding alkali, which establishes the reactions as unimolecular.

TABLE 1.—*The rate of solvolysis of* 3 : 4 : 6-*tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucosyl* 1-*chloride and* 3 : 4 : 6-*tri*-O-*acetyl*-β-D-*glucosyl* 1-*chloride in various media.*

| Medium | Temp. | $10^5k_1$(sec.$^{-1}$) | Medium | Temp. | $10^5k_1$(sec.$^{-1}$) |
|---|---|---|---|---|---|
| Tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl 1-chloride | | | 3 : 4 : 6-Tri-*O*-acetyl-β-glucosyl 1-chloride | | |
| MeOH | 21·2° | 1·18 | MeOH | 21·2° | 66·6 |
| ,, | 27·4 | 2·48 | ,, | 34·8 | 229 |
| ,, | 34·9 | 3·48 | 80% Aq. $COMe_2$ | 21·2 | 24·6 |
| 90% Aq. MeOH | 27·4 | 6·74 | 60% ,, | 21·2 | 120 |
| 80% ,, | 27·4 | 11·79 | ,, ,, | *ca.* 24 | 195 * |
| 90% MeOH–$COMe_2$ | 27·4 | 1·34 | ,, ,, | *ca.* 24 | 196 * † |
| 80% ,, | 27·4 | 1·02 | | | |
| 60% ,, | 27·4 | 0·48 | | | |
| 80% Aq. $COMe_2$ | 34·9 | 0·61 | | | |
| 60% ,, | 34·9 | 5·64 | | | |
| ,, ,, | 18 | 1·41 * | | | |
| ,, ,, | 18 | 1·44 * † | | | |

* Measurements made simultaneously by the polarimetric method.
† [Alkali] = 0·025N.

The Arrhenius activation energy for the methanolysis of tri-*O*-acetyl-2-trichloroacetyl-β-D-glucosyl 1-chloride is 20·8 kcal., whereas that for 3 : 4 : 6-tri-*O*-acetyl-β-D-glucosyl

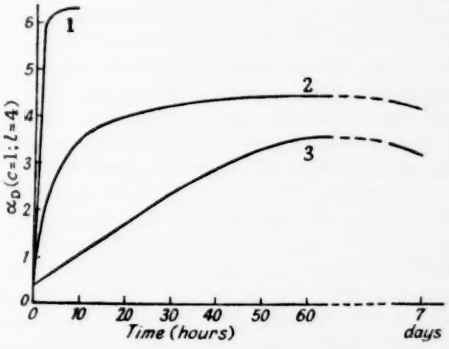
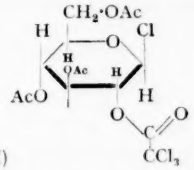



FIG. 1. *Methanolysis of* 3 : 4 : 6-*tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucosyl* 1-*chloride and* 3 : 4 : 6-*tri*-O-*acetyl*-β-D-*glucosyl* 1-*chloride.*

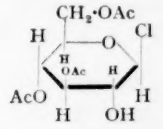
1, 3 : 4 : 6-*Tri*-O-*acetyl*-β-D-*glucosyl* 1-*chloride in* 100% MeOH.
2, 3 : 4 : 6-*Tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucosyl* 1-*chloride in* 80% *aqueous* MeOH.
3, *As* 2, *but in* 100% MeOH.

1-chloride is 16·3 kcal., a value deduced from measurements at two temperatures only and so subject to error. The lower reactivity of the 2-trichloroacetyl derivative is largely due to this increase in the activation energy of the reaction.

The products of the reaction of the two compounds with alcohols were fully studied by Hickinbottom (*J.*, 1929, 1676) whose results show that during certain reactions racemisation had occurred. Tri-*O*-acetyl-2-trichloroacetyl-β-D-glucosyl 1-chloride, for example, with methanol in the presence of silver carbonate gave 70% of α- and 30% of β-methyl




(I)




(II)

glucoside, whereas in the corresponding reaction of 3 : 4 : 6-tri-*O*-acetyl-β-D-glucosyl 1-chloride the product was almost completely the α-glucoside. This result was confirmed by a polarimetric examination of the reaction. In Fig. 1 is shown the variation of optical rotation during the reaction of (I) and (II) with methanol. From the much higher value of the rotation in the second case, the presence of a higher proportion of α-isomer may be inferred. With the 2-trichloroacetyl derivative (I) it was noted that the addition of

water had an effect similar to that observed with tetra-*O*-acetyl-α-D-glucosyl 1-bromide (Part I, *loc. cit.*). It is not unexpected that the alcoholysis of tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl 1-chloride leads to a certain amount of β-glucoside since the large trichloroacetyl group would exert a shielding influence on the side at which the entering group leads to the formation of the α-glucoside. 3 : 4 : 6-Tri-*O*-acetyl-β-D-glucosyl 1-chloride, on the other hand, in which the hydroxyl group at $C_{(2)}$ is not acylated is able to produce the α-glucoside in the normal manner. Although discussion of the formation of 1 : 2-orthoesters is being reserved for a subsequent communication, it is pertinent that it does not occur in solvolysis of the 2-trichloroacetyl compound. Although the acyl group is *trans* to the halogen atom at $C_{(1)}$, the inductive effect of the trichloromethyl group will so diminish the polarisation of the carbonyl group that the cyclic orthoester cation is not formed. Although both compounds (I) and (II) undergo solvolysis by the unimolecular mechanism, that of (II) with methanol is over 60 times as fast at 21° as that of (I). This demonstrates the large steric effect operating here.

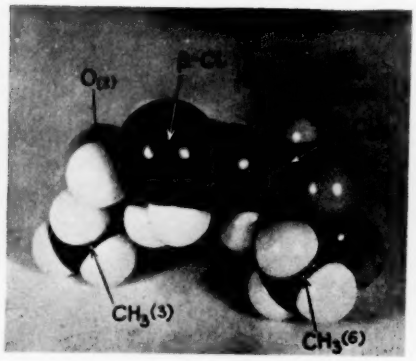
In order to ascertain the extent to which each acetyl group affects the reactivity of the halogen atom, a systematic variation of the configuration of the groups in the molecule was undertaken by choosing appropriate compounds.

*The Acetyl Group at* $C_{(2)}$.—A change in configuration at position 2 to make the acetyl group *trans* to the 1-halogen atom in the α-configuration is found in the mannose series. In Table 2 the rate constant for the methanolysis of tetra-*O*-acetyl-α-D-mannosyl 1-bromide (III) is given and, compared with tetra-*O*-acetyl-α-D-glucosyl 1-bromide at the same temperature, there is a ten-fold increase in the solvolysis rate. To confirm the unimolecular character of the reaction, the effect of alkali on the solvolysis in 60% aqueous acetone was examined and only a small increase in rate was observed. The amount of alkali used was insufficient to maintain alkalinity throughout the reaction and it became acidic during the measurements; nevertheless this had no effect on the kinetic form of the reaction. It is safe to conclude therefore that the solvent molecules do not function as reagents in the rate-determining stage of the reaction.

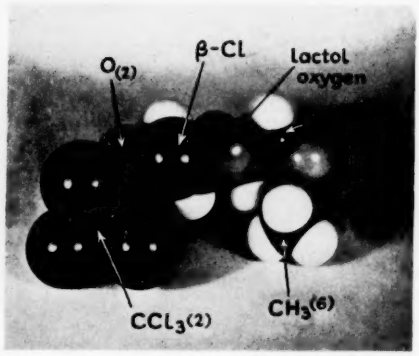
*The Acetyl Group at* $C_{(3)}$.—In the present series the effect of the acetyl group at position 3 could not be ascertained. A change of configuration at this position gives allose, and neither this sugar nor its appropriate derivatives were available. Howard (*J.*, 1950, 1045), however, has suggested that in a *cis*-2 : 3-diacetoxy-system, the 3-acetoxy-group would restrict the movement of the 2-acetoxy-group to the neighbourhood of $C_{(1)}$, and examination of scale models showed that this effect is likely in the *trans*-system also.

*The Acetyl Group at* $C_{(4)}$.—If the configuration of *O*-glucose is inverted at position 4, D-galactose results. A first-order rate constant for the methanolysis of tetra-*O*-acetyl-α-D-galactosyl 1-bromide (IV) was obtained by both the polarimetric method and titration of the acid liberated with standard alkali (Table 2). Catalysis by liberated acid was noticed during the later stages of the reaction. The rate of methanolysis of this derivative is 4·5 times greater than that of the corresponding glucose compound, an increase which can only be attributed to the acetyl group at $C_{(4)}$. Solvent effects were observed similar to those with tetra-*O*-acetyl-α-D-glucosyl 1-bromide. A change of medium from 80% to 60% aqueous acetone produced an eight-fold increase in rate, compared with a nine-fold increase for the glucose derivative. The possibility of a bimolecular reaction was again eliminated by the failure of added alkali to affect the rate constant in 60% aqueous acetone (Table 2).

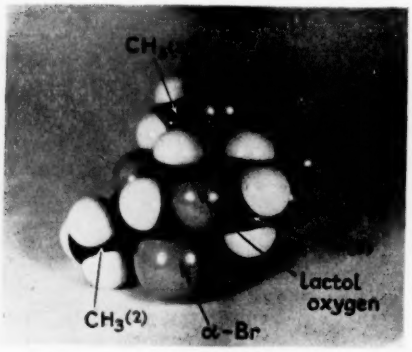
*Position* 6. *The Acetoxymethyl Group.*—There is little doubt that $C_{(1)}$ and $C_{(6)}$ can approach each other in some substituted compounds since 1 : 6-anhydrides can be formed. For instance, tetra-*O*-acetyl-α-glucosyl 1-bromide reacts with trimethylamine, to give a quaternary bromide from which 1 : 6-anhydro-β-D-glucose is formed by treatment with barium hydroxide solution (Micheel, *Ber.*, 1929, **62**, 687; Karrer and Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 819); and 1 : 6-anhydro-β-D-galactose is obtained in a similar way. It was therefore expected that the acetoxymethyl group in the hexose series would influence the properties of the 1-halogen atom. A direct experimental test was made by investigating tri-*O*-acetyl-α-D-xylosyl 1-bromide (V) in which, apart from the absence of the acetoxymethyl group attached to $C_{(5)}$, the rest of the molecule is identical with the glucosyl bromide.



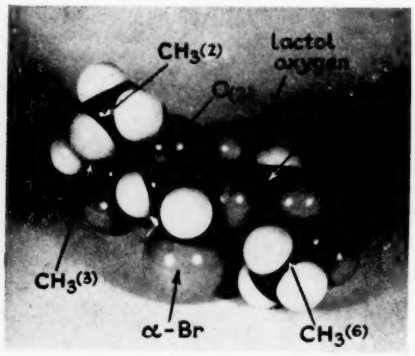

1, 3 : 4 : 6-*Tri*-O-*acetyl*-β-D-*glucosyl* 1-*chloride*.



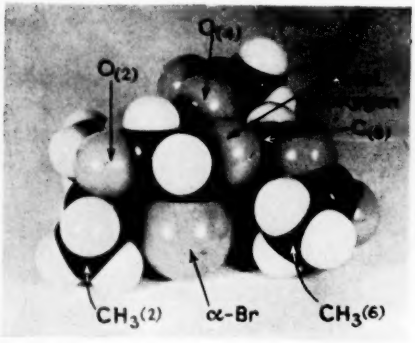

2, 3 : 4 : 6-*Tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucosyl* 1-*chloride*.



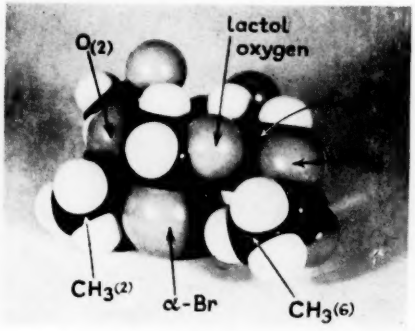

3, *Tri*-O-*acetyl*-α-D-*xylosyl* 1-*bromide*.




4, *Tetra*-O-*acetyl*-α-D-*mannosyl* 1-*bromide*.



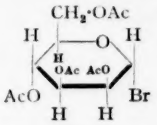

5, *Tetra*-O-*acetyl*-α-D-*galactosyl* 1-*bromide*.



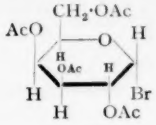

6, *Tetra*-O-*acetyl*-α-D-*glucosyl* 1-*bromide*.

[*To face p.* 2967.

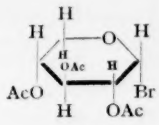
The methanolysis rate was found to be 50 times greater than that of the glucose derivative (Table 2)—a striking confirmation of the prediction by Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929) that tetra-*O*-acetylxylosyl bromide should be more reactive than the glucose derivative. As with tetra-*O*-acetyl-α-D-mannosyl 1-bromide, there was a small increase in rate of the solvolysis in 60% aqueous acetone in the presence of alkali. Here again, the possibility of a bimolecular reaction could be eliminated because no change in kinetic form was observed when the alkali had been consumed and the medium became acidic.



(III)



(IV)



(V)

The foregoing experiments show that the geometrical position of the acetyl groups has a pronounced effect on the reactivity of the halogen atom which throughout follows a unimolecular mechanism in solvolysis. Since the conventional sugar formulæ give no indication of the size of the groups or of their disposition in the molecule, it was necessary to consider the more precise structure of the *O*-acetylglycosyl 1-halides which have been investigated. This was done by assigning a ring conformation and then, with the aid of accurate scale models and consideration of the intramolecular interactions in the molecule,

TABLE 2. *Comparison of the rate of solvolysis of several* O-*acetyl-*α*-glycosyl* 1-*halides with that of tetra*-O-*acetyl-*α*-glucosyl* 1-*bromide.*

| Tetra-*O*-acetyl-α-D-glycosyl 1-bromide | Medium | Temp. | $10^5k_1$ (sec.$^{-1}$) | Tetra-*O*-acetyl-α-D-glycosyl 1-bromide | Medium | Temp. | $10^5k_1$ (sec.$^{-1}$) |
|---|---|---|---|---|---|---|---|
| Glucosyl ... | MeOH | 21·2° | 2·80 | Galactosyl | MeOH | 21·2° | 12·4 |
| Mannosyl ... | MeOH | 21·2 | 30·0 | | ,, | 35·0 | 45·3 |
| | 60% Aq. $COMe_2$ | 16 | 13·1 * | | ,, | 16 | 8·5 * |
| | ,, ,, | 16 | 16·9 † | | 80% Aq. $COMe_2$ | 21·2 | 1·69 |
| Xylosyl ..... | MeOH | 21·2 | 139 * | | 60% ,, | 21·2 | 13·5 |
| | ,, ,, | 16 | 94 * | | ,, ,, | 21 | 13·7 * |
| | 60% Aq. $COMe_2$ | 16 | 76·3 * | | ,, ,, | 21 | 13·7 * † |
| | ,, ,, | 16 | 82·0 * † | | | | |

* Polarimetric method employed.
† [Alkali] = 0·025N; measurements were made at the same time as those in which alkali was absent.

the most likely relative arrangement of the substituent groups was determined. The *cyclo*hexane molecule has been shown by many workers (Hermanns, *Rec. Trav. chim.*, 1938, **57**, 333; Kohlrausch and Wittek, *Z. physikal. Chem.*, 1941, **48**, *B*, 177; Geoding, Smit, and Westrik, *Rec. Trav. chim.*, 1942, **61**, 561; Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63**, 2029; Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488) to exist predominantly in the rigid chair form. A similar conclusion has been drawn concerning the ring conformation in the pyranose form of the sugars, both from theoretical (Gorin, Kanzmann, and Walter, *J. Chem. Phys.*, 1939, **7**, 327; Cox, *J.*, 1935, 1495) and experimental considerations (Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 215, 1737; *Adv. Carbohydrate Chem.*, 1952, **6**, 108). From a study of the cuprammonium–glycoside complexes Reeves reduced the number of possible conformations to not more than three and in the sugars under discussion the conformation at $C_{(1)}$ (Fig. 2) is sufficient to explain their behaviour as complex-forming glycosides. This is assumed to be present in the *O*-acylglycosyl 1-halides and was adopted in the models. In the acetyl group, the carbonyl charge distribution $>C\overset{\curvearrowright}{=}O$ is well established and hyperconjugation permits allocation of a fractional positive charge to the hydrogen atoms of the methyl group. The other polar link in the *O*-acylglycosyl 1-halides is $C_{(1)}$–Hal. In the models constructed, the groups

were assigned to positions based on these fractional charges, so that the resultant molecule would have the minimum potential energy, a methyl group for example being directed towards a carbonyl-oxygen atom. By means of this convention, the precise structures of the *O*-acylglycosyl 1-halides were built up (Phillips, Thesis, University of Wales, 1952). The various structures are illustrated in the Plate and it is seen that each presents a different amount of hindrance in the neighbourhood of the halogen atom. A correlation between this variation in steric hindrance and rate of methanolysis is shown in Table 3. As the hindrance at $C_{(1)}$ increases so does the rate constant decrease.

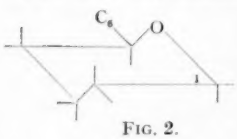
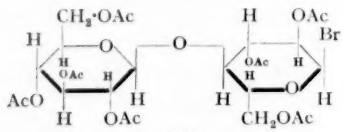


FIG. 2.

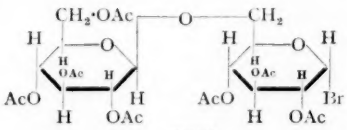
TABLE 3. *Variation in rate constant with steric hindrance.*

| Compound | Hindrance at $C_{(1)}$ | Relative rate constant |
|---|---|---|
| Tri-*O*-acetyl-α-D-xylosyl 1-bromide | Least | 50 |
| Tetra-*O*-acetyl-α-D-mannosyl 1-bromide | ↓ | 10 |
| Tetra-*O*-acetyl-α-D-galactosyl 1-bromide | ↓ | 4·5 |
| Tetra-*O*-acetyl-α-D-glucosyl 1-bromide | Greatest | 1 |

Further confirmation that the variation in unimolecular solvolysis rate is a direct function of the steric hindrance at $C_{(1)}$ was obtained from a study of hepta-*O*-acetyl-α-cellobiosyl 1-bromide (VI) and hepta-*O*-acetyl-α-gentiobiosyl 1-bromide (VII). These may



(VI)



(VII)

be considered as tetra-*O*-acetylglucosyl 1-bromide in which an acetylated glucosyl residue has been substituted at position 4 or 6. Examination of their scale models showed that the orientation of the groups in the neighbourhood of the halogen is similar to that in tetra-*O*-acetyl-α-D-glucosyl 1-bromide, except that in the gentiobiose derivative it is slightly less because of the biose linkage at position 6. The first-order constants for their methanolysis are compared in Table 4 and completely support the relation between steric hindrance and reactivity.

TABLE 4. *Methanolysis of hepta-*O*-acetyl-α-cellobiosyl 1-bromide, hepta-*O*-acetyl-α-gentiobiosyl 1-bromide and tetra-*O*-acetyl-α-glucosyl 1-bromide at 35°.*

| Compound | $10^4 k_1$ (sec.$^{-1}$) |
|---|---|
| Tetra-*O*-acetyl-α-glucosyl 1-bromide | 1·21 |
| Hepta-*O*-acetyl-α-cellobiosyl 1-bromide | 1·12 |
| Hepta-*O*-acetyl-α-gentiobiosyl 1-bromide | 2·98 |

## EXPERIMENTAL

*Materials.*—3 : 4 : 6-Tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl 1-chloride, m. p. 139—140°, was prepared by the action of phosphorus pentachloride on β-penta-*O*-acetylglucose (Brigl, *Z. physiol. Chem.*, 1921, **116**, 1; Hickinbottom, *J.*, 1929, 1676; Abramovitch, *J.*, 1951, 2996). The purity of the phosphorus pentachloride noted by Farrar (*J.*, 1949, 3131) was not found to be important, but no product was obtained when the α-penta-acetate was used. Selective deacylation gave 3 : 4 : 6-tri-*O*-acetyl-β-D-glucosyl 1-chloride, m. p. 153—155° (after five recrystallisations from ethyl acetate) (Brigl; Hickinbottom, *locc. cit.*). The *O*-acetylglycosyl 1-bromides were prepared from the sugar acetates by the standard procedure. Tetra-*O*-acetyl-α-D-galactosyl 1-bromide had m. p. 82—83°, $[\alpha]_D^{20}$ +237° (*c*, 1·22 in benzene). Tri-*O*-acetyl-α-*O*-xylosyl 1-bromide had m. p. 100—101°, $[\alpha]_D^{20}$ +210° (*c*, 1·17 in $CHCl_3$); to avoid decomposition it was kept under ether until required. Tetra-*O*-acetyl-α-D-mannosyl 1-bromide could not be crystallised. Isolated by methods of Micheel and Micheel (*Ber.*, 1930, **63**, 386) and Levene and Tipson (*J. Biol. Chem.*, 1931, **90**, 89) the products showed $[\alpha]_D^{20}$

+111·2° and 115·6° (*c*, 1·64 and 1·37 in $CHCl_3$) (Found : Br, 19·0 and 19·3. Calc. for $C_{14}H_{19}O_9$ : Br, 19·5%). Hepta-*O*-acetyl-α-cellobiosyl 1-bromide and hepta-*O*-acetyl-α-gentiobiosyl 1-bromide had respectively m. p. 180° and 143—144° and $[\alpha]_D^{20}$ +95·4° (*c*, 1·26 in $CHCl_3$) and $[\alpha]_D^{18}$ +100·3° (*c*, 1·46 in $CHCl_3$).

Solvents were purified by the methods described in the preceding papers.

*Rate Measurements.*—The technique was the same as that employed in the preceding papers. The following record of detailed experiments is typical of the series of solvolytic reactions studied. The concentration of the halides is expressed in equivalent ml. of standard alcoholic alkali per 5 ml. of solution, and the first-order rate constants are in sec.$^{-1}$.

*Methanolysis of the* O-*acylglycosyl* 1-*halides at* 21·2° (*except where otherwise stated*).

3 : 4 : 6-*Tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucosyl* 1-*chloride*

| *t* (min.) | 0 | 50 | 80 | 140 | 270 | 330 | 450 | 500 | 575 |
|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 8·70 | 8·35 | 8·10 | 7·87 | 7·22 | 6·85 | 6·31 | 6·10 | 5·79 |

[Halide] = 0·0216M. Alkali = 0·025N. Slope : $-3·07 \times 10^{-4}$ min.$^{-1}$. $10^5k = 1·18$.

*Tetra*-O-*acetyl*-α-D-*mannosyl* 1-*bromide* (21·3°)

| *t* (min.) | 0 | 2 | 5 | 10 | 20 | 25 | 30 | 35 | 40 | 45 | 50 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 8·40 | 7·41 | 7·02 | 6·40 | 5·43 | 4·90 | 4·43 | 4·12 | 3·76 | 3·43 | 3·14 |

[Halide] = 0·0252M. Alkali = 0·0151N. Slope : $-7·80 \times 10^{-3}$ min.$^{-1}$. $10^4k = 3·00$.

*Tri*-O-*acetyl*-α-D-*xylosyl* 1-*bromide*.

| *t* (min.) | 0 | 2 | 5 | 7·5 | 10 | 12 | 15 | 17·5 | 20 | 22 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 12·00 | 10·35 | 8·33 | 6·53 | 5·27 | 4·47 | 3·25 | 2·82 | 2·21 | 1·95 | 1·51 |

[Halide] = 0·0247M. Alkali = 0·0102N. Slope : $-3·61 \times 10^{-2}$ min.$^{-1}$. $10^3k = 1·39$.

*Hepta*-O-*acetyl*-α-*gentiobiosyl* 1-*bromide* (35·0°).

| *t* (min.) | 0 | 4 | 10 | 12·5 | 15 | 19 | 25 | 30 | 35 | 40 | 50 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [Halide] | 5·66 | 5·35 | 4·87 | 4·61 | 4·45 | 4·11 | 3·71 | 3·39 | 3·10 | 2·76 | 2·37 |

[Halide] = 0·011M. Alkali = 0·010N. Slope : $-7·75 \times 10^{-3}$ min.$^{-1}$. $10^4k = 2·98$.

Certain reactions (Tables 1 and 2) were followed polarimetrically according to the details given in Part I. The following results are typical.

*Solvolysis of tetra*-O-*acetyl*-α-D-*galactosyl* 1-*bromide in* 60% *aqueous acetone at* 21°.

| *t* (min.) | 7 | 15 | 30 | 40 | 65 | 80 | 105 | 125 | 160 | 180 | 220 | ∞ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α | 4·62° | 4·42° | 3·98° | 3·79° | 3·41° | 3·21° | 2·89° | 2·68° | 2·34° | 2·18° | 1·93° | 1·35° |

*c*, 1·0875. *l* = 2. Slope : $-3·575 \times 10^{-3}$ min.$^{-1}$. $10^4k = 1·37$.

*The same containing* 0·03N-*alkali*.

| *t* (min.) | 5 | 15 | 30 | 45 | 60 | 85 | 110 | 140 | 180 | 200 | 220 | ∞ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α | 3·51° | 3·28° | 3·03° | 2·87° | 2·70° | 2·43° | 2·23° | 1·97° | 1·76° | 1·66° | 1·60° | 1·21° |

*c*, 1·1565. *l* = 2. Slope : $-3·576 \times 10^{-3}$ min.$^{-1}$. $10^4k = 1·37$.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, March 27th*, 1953.]

## 582. *Quinones. Part III.* Addition Reactions of* 1 : 4-*Naphthaquinones substituted in the* 6-*Position.*

By J. M. Lyons and R. H. Thomson.

The addition of aniline, acetic anhydride, toluene-*p*-thiol, and bromine to 6-hydroxy-, 6-acetoxy-, 6-methyl-, 6-chloro-, and 6-acetamido-1 : 4-naphthaquinone has been studied and the majority of the products orientated. The substituent has a marked effect on the course of the reactions, resulting in the predominant formation of one isomer in all cases except the additions of toluene-*p*-thiol. The reactions with aniline and bromine readily gave single products and are of value for synthetic purposes. The direction of addition of aniline and acetic anhydride is in accord with the electronic character of the 6-substituent, but the latter exerts no control over the addition of toluene-*p*-thiol. The reactions with bromine were anomalous.

Addition reactions are a characteristic feature of the chemistry of quinones, and many derivatives can be conveniently obtained in this way, *e.g.*, hydroxyquinones are readily available *via* the addition of amines or acetic anhydride. However, these methods are of less value in unsymmetrical quinones where more than one product may result. This is the case with monobenzo-derivatives of 1 : 4-naphthaquinones and synthetic work in this field would be assisted if more information were available about the course of addition to such compounds. A study of addition reactions with 5-hydroxy- and 5-acetoxy-1 : 4-naphthaquinone revealed some unexpected results (Thomson, *J. Org. Chem.*, 1951, **16**, 1082) but very little is known concerning the addition reactions of 6-substituted 1 : 4-naphthaquinones. Fieser and Brown (*J. Amer. Chem. Soc.*, 1949, **71**, 3615) obtained two products by Thiele acetylation of 6-chloro-1 : 4-naphthaquinone whereas Kegel (*Annalen*, 1888, **247**, 187) by addition of aniline and *p*-toluidine to 6-benzoyl-1 : 4-naphthaquinone obtained only one amino-derivative in each case. It is evident from the latter work that the 6-substituent can have a pronounced effect on the reaction taking place in the quinone ring, and a study of some addition reactions of 6-hydroxy-, 6-acetoxy-, 6-methyl-, 6-chloro-, and 6-acetamido-1 : 4-naphthaquinone has now confirmed this.† The reagents used were aniline (a typical nucleophilic reagent), acetic anhydride (which gives an acid-catalysed electrophilic reaction) and toluene-*p*-thiol (this reagent appears to add to 5-hydroxy- and 5-acetoxy-1 : 4-naphthaquinone by a radical mechanism). The formation of bromoquinones by the addition of bromine and elimination of hydrogen bromide from the dibromides was also investigated. The results are set out in the Table. The products were isolated by conventional methods and mother-liquors, etc., were not exhaustively searched. Thus the isolation of only one isomer does not exclude the formation of another in small amount, but we were mainly concerned with the preparative value of these reactions. From this point of view the reactions with aniline and bromine are of value as single products were readily isolated in a pure state, whereas the reactions with acetic anhydride and toluene-*p*-thiol led to mixtures and separation was frequently tedious, involving appreciable loss.

The results bear out earlier suggestions put forward to account for the influence of benz-substituents in 1 : 4-naphthaquinones (Thomson, *loc. cit.*; Cooke and Segal, *Austral. J. Sci. Res.*, 1950, *A*, **3**, 628). In the addition reactions with aniline and acetic anhydride one isomer predominates, electron-repelling substituents at $C_{(6)}$ directing entering groups to $C_{(2)}$, whereas in 6-chloro-1 : 4-naphthaquinone reaction is mainly at $C_{(3)}$. We consider therefore that Kegel's compounds (*loc. cit.*) are probably 3-arylamino-6-benzoyl-1 : 4-naphthaquinones. In contrast the reactions with toluene-*p*-thiol gave roughly equal amounts of the two isomers in all cases, which again suggests a radical mechanism as substituents at $C_{(6)}$ have little effect on the course of the reaction. The

* Part II, *J.*, 1953, 1138.

† Since this paper was submitted we have seen a publication by Cooke, Dowd, and Segal (*Austral. J. Chem.*, 1953, **6**, 38) who show that addition of dimethylamine to 6-methyl-1 : 4-naphthaquinone yields 2-dimethylamino-6-methyl-1 : 4-naphthaquinone and possibily a small amount of the 3-isomer.

reactions with bromine are anomalous and in several instances we failed to isolate the initial adduct.

*Products obtained by addition to* 6-*substituted* 1 : 4-*naphthaquinones.*

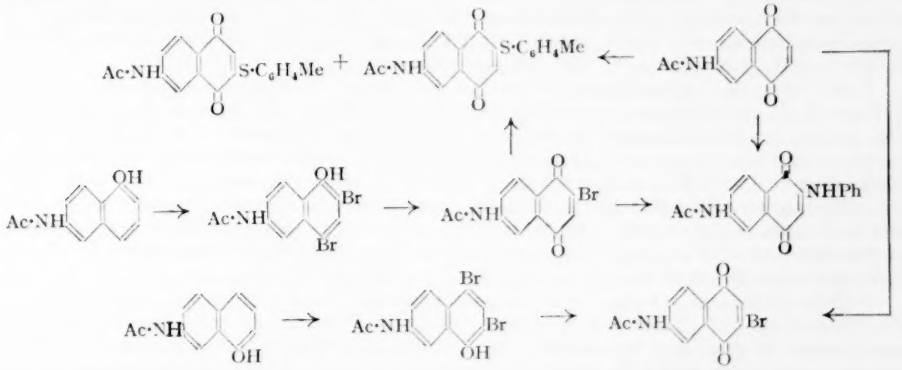
| 6-Substituent | $NH_2Ph$ [1] | *p*-$C_6H_4Me{\cdot}SH$ [1] | Br [2] | $Ac_2O$ [3] |
|---|---|---|---|---|
| | Orientation * and yield of compound(s) produced by | | | |
| OH | **2** (88%) | *x* (37%); *y* (34%) | **2** (70%) | — |
| OAc | **2** (83%) | *x* (38%); *y* (31%) | **2** (60%) | **2** (58%); **3** (8%) |
| Me | **2** (78%) | **2** (36%); **3** (30%) | **3** (78%) | **2** (?62%); **3** (?7%) |
| Cl | **3** (84%) | *x* (36%); *y* (49%) | **3** (81%) | **2** (36%); **3** (49%) |
| NHAc | **2**( 89%) | **2** (42%; **3** (31%) | **3** (67%) | — |

* $x = 2$, and $y = 3$, or *vice versa*.

[1] Yields are for the quinones obtained by oxidation of the initial adduct. [2] Yields are for the bromoquinones obtained by elimination of hydrogen bromide from the initial adduct. [3] Yields are for the triacetoxynaphthalenes obtained by complete reaction with acetic anhydride.

*Orientation of the Products.*—6-*Hydroxy*-1 : 4-*naphthaquinone.* Hydrolysis of the anilino-derivative yielded the known 2 : 6-dihydroxy-1 : 4-naphthaquinone, reductive acetylation of which gave 1 : 2 : 4 : 6-tetra-acetoxynaphthalene identical with the product obtained by Dimroth and Kerkovius (*Annalen*, 1913, **399**, 37) by Thiele acetylation of 6-hydroxy-1 : 2-naphthaquinone. The identity of the bromo-6-hydroxy-1 : 4-naphthaquinone was determined by reaction with aniline which gave 2-anilino-6-hydroxy-1 : 4-naphthaquinone. The toluene-*p*-thio-derivatives could not be orientated either by replacement reactions or by alternative methods of preparation. The acetates of all the above compounds were obtained both by acetylation and by the corresponding addition reactions with 6-acetoxy-1 : 4-naphthaquinone. The products of Thiele acetylation were compared with authentic specimens.

6-*Methyl*-1 : 4-*naphthaquinone.* Hydrolysis of the anilino-derivative gave the known 2-hydroxy-6-methyl-1 : 4-naphthaquinone. The structure of the bromo-derivative was established by reaction with hydrochloric acid to give a chloroquinone which was different from that obtained by treatment of 2-hydroxy-6-methyl-1 : 4-naphthaquinone with thionyl chloride. Two toluene-*p*-thiol addition products were obtained, one of which was also prepared from 3-bromo-6-methyl-1 : 4-naphthaquinone by reaction with toluene-*p*-thiol. Thiele acetylation gave a mixture of acetates which was converted into a mixture of hydroxymethylnaphthaquinones; neither mixture could be separated. Evidence was obtained (see Experimental section) which indicated that the major product was 1 : 2 : 4-triacetoxy-6-methylnaphthalene.




6-*Chloro*-1 : 4-*naphthaquinone.* The structures of the Thiele acetylation products were established by Fieser and Brown (*loc. cit.*). 1 : 3 : 4-Triacetoxy-6-chloronaphthalene was also obtained by hydrolysis of the anilino-derivative followed by reductive acetylation. Reaction of the bromo-compound with hydrochloric acid gave a dichloroquinone identical with that obtained from 6-chloro-3-hydroxy-1 : 4-naphthaquinone with the aid of thionyl

chloride, and different from 2 : 6-dichloro-1 : 4-naphthaquinone (Claus and Müller, *Ber.*, 1885, **18**, 3073). The two 6-chloro-*p*-tolylthio-1 : 4-naphthaquinones were not identified.

*6-Acetamido-1 : 4-naphthaquinone.* This quinone was less reactive than the others, and the products were relatively less soluble and of higher melting point. The orientations in this group were based on the 2- and 3-bromo-derivatives. These were obtained by bromination of 6- and 7-acetamido-1-naphthol to dibromo-compounds, which were oxidised to monobromoacetamido-1 : 4-naphthaquinones. One of these was also obtained by bromination of 6-acetamido-1 : 4-naphthaquinone, and the other contained a reactive bromine atom replaceable by aniline. Thus bromination occurred exclusively in the hydroxylated ring of the acetamidonaphthols. One of the toluene-*p*-thiol addition products was also obtained from the 2-bromo-derivative. These reactions are set out in the annexed scheme. Thiele acetylation of 6-acetamido-1 : 4-naphthaquinone was unsuccessful with concentrated sulphuric acid or boron trifluoride–ether complex as catalyst; some reaction took place in the presence of perchloric acid, but was difficult to reproduce. The product obtained, in poor yield, appeared to be a single compound but has not been identified

## Experimental

*6-Hydroxy-1 : 4-naphthaquinone.*—Recorded preparations (Fischer and Bauer, *J. pr. Chem.*, 1916, **94**, 1; Dimroth and Roos, *Annalen*, 1927, **456**, 185) utilise 1 : 6-dihydroxynaphthalene as starting material. By a similar procedure we coupled 1-amino-7-naphthol with diazotised sulphanilic acid in acid solution, reduced the azo-compound with zinc dust and hydrochloric acid, and subsequently oxidised the diamino-naphthol with ferric chloride. The quinone crystallised from water in orange needles, m. p. 170° (decomp.) (20%). The *acetate* formed pale yellow needles, m. p. 102° (from aqueous methanol) (Found: C, 66·6; H, 4·0. $C_{11}H_8O_4$ requires C, 66·7; H, 3·7%). Fischer and Bauer (*loc. cit.*) prepared this compound but did not describe it.

*2-Anilino-6-hydroxy-1 : 4-naphthaquinone.*—(*a*) 6-Hydroxy-1 : 4-naphthaquinone (1·5 g.) in alcohol (20 c.c.) was refluxed with aniline (0·8 g.) for 10 min. and allowed to cool overnight. The crystalline product was collected and more was obtained by concentration of the reaction liquor. Recrystallisation from acetic acid afforded the *anilino-quinone* as dark red needles, m. p. 302° (88%). (*b*) A mixture of 2-bromo-6-hydroxy-1 : 4-naphthaquinone (1 g.), aniline (0·4 c.c.), and alcohol (40 c.c.) was boiled for 1 hr. and then diluted with water. On cooling, dark red needles, m. p. 294° (63%), separated. Recrystallisation gave crystals indistinguishable from those described in (*a*) (Found: C, 72·4; H, 4·4; N, 5·0. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·2; N, 5·3%). The *acetate* was obtained by cold acetylation in pyridine and by addition of aniline to 6-acetoxy-1 : 4-naphthaquinone according to the above procedure (83%). It crystallised from aqueous acetic acid in light red crystals, m. p. 205° (Found: C, 70·1; H, 4·1; N, 4·7. $C_{18}H_{13}O_4N$ requires C, 70·4; H, 4·2; N, 4·55%).

*2 : 6-Dihydroxy-1 : 4-naphthaquinone.*—To a solution of 2-anilino-6-hydroxy-1 : 4-naphthaquinone (1 g.) in concentrated sulphuric acid (10 c.c.), water (10 c.c.) was added cautiously. The mixture was brought to the boil and then poured into water (50 c.c.). The crude dihydroxyquinone which was precipitated was extracted with aqueous sodium acetate (2%) and crystallised from acetic acid as yellow needles which decomposed gradually between 100° and 200° (77%). The diacetate formed yellow plates, m. p. 163° (from alcohol) (this was prepared by Dimroth and Kerkovius, *Annalen*, 1913, **339**, 36, who did not record the m. p.). Reductive acetylation of the diacetate with zinc dust, acetic anhydride, and a drop of pyridine yielded 1 : 2 : 4 : 6-tetra-acetoxynaphthalene in needles, m. p. and mixed m. p. 184°.

*6-Hydroxy-2- and -3-p-tolylthio-1 : 4-naphthaquinone.*—A solution of 6-hydroxy-1 : 4-naphthaquinone (0·5 g.) and toluene-*p*-thiol (0·3 g.) in alcohol (20 c.c.) was kept at room temperature for 30 min. and then oxidised by addition of sodium dichromate (0·5 g.) in water (20 c.c.) containing concentrated sulphuric acid (0·3 c.c.). Fractional crystallisation from acetic acid yielded two *products*: (*a*) less soluble orange-yellow needles, m. p. 247—251° (37%) and (*b*) more soluble orange-yellow crystals, m. p. 208° (34%) [Found: (*a*) 68·6; H, 4·2; S, 10·5; (*b*) C, 68·85; H, 4·2; S, 10·8. $C_{17}H_{12}O_3S$ requires 68·9; H, 4·0; S, 10·8%). These gave *acetates*, (*a*) yellow crystals, m. p. 175° (from acetic acid) and (*b*) small yellow needles, m. p. 155° (from aqueous alcohol) [Found: (*a*) C, 67·5; H, 4·2; S, 9·15; (*b*) C, 67·6; H, 4·3; S, 9·2. $C_{19}H_{14}O_4S$ requires C, 67·45; H, 4·15; S, 9·45%). The two acetates were

also obtained by addition of toluene-*p*-thiol to 6-acetoxy-1 : 4-naphthaquinone by the same procedure and were separated by fractional crystallisation from acetic acid.

2-*Bromo*-6-*hydroxy*-1 : 4-*naphthaquinone*.—A solution of bromine (1·6 g.) in acetic acid (5 c.c.) was added to one of 6-hydroxy-1 : 4-naphthaquinone (1·7 g.) in acetic acid (40 c.c.). After 10 min. the solution was poured on to ice-water (200 c.c.) and set aside for several hours. The *bromohydroxyquinone* slowly separated and was crystallised from acetic acid, forming yellow needles, m. p. 188° (70%) (Found : C, 47·6; H, 2·3; Br, 31·1. $C_{10}H_5O_3Br$ requires C, 47·4; H, 2·0; Br, 31·6%). The *acetate* formed yellow needles, m. p. 120° (Found : C, 48·8; H, 2·6; Br, 26·8. $C_{12}H_7O_4Br$ requires C, 48·8; H, 2·4 : Br, 27·1%). This compound was also obtained by bromination of 6-acetoxy-1 : 4-naphthaquinone by the above procedure (60%); again no dibromide was isolated.

1 : 2 : 4 : 6- *and* 1 : 3 : 4 : 6-*Tetra-acetoxynaphthalenes*.—6-Hydroxy-1 : 4-naphthaquinone (0·5 g.) in acetic anhydride (4 c.c.) was treated with two drops of concentrated sulphuric acid. After 5 days the mixture was diluted with water, and the precipitate obtained was recrystallised from aqueous methyl alcohol. Two fractions were isolated : (*a*) less soluble needles, m. p. 184—185° (58%), and (*b*) more soluble crystals, m. p. 139° (after several crystallisations from light petroleum) (8%) (Found : C, 60·3; H, 4·7. Calc. for $C_{18}H_{16}O_8$ : C, 60·0; H, 4·5%). Mixed m. p. determinations with authentic specimens established that (*a*) was 1 : 2 : 4 : 6- and (*b*) 1 : 3 : 4 : 6-tetra-acetoxynaphthalene.

2-*Anilino*-6-*methyl*-1 : 4-*naphthaquinone*.—6-Methyl-1 : 4-naphthaquinone (1 g.) and aniline (0·5 c.c.) were refluxed in ethyl alcohol (20 c.c.) for 1 hr., and the *product* collected next morning. It formed red crystals, m. p. 206° (from aqueous acetic acid) (78%) (Found : C, 77·7; H, 5·2; N, 4·9. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 5·0; N, 4·9%).

2-*Hydroxy*-6-*methyl*-1 : 4-*naphthaquinone*.—A solution of 2-anilino-6-methyl-1 : 4-naphthaquinone (0·5 g.) in concentrated sulphuric acid (4 c.c.) was diluted with water (4 c.c.), boiled for 1 min., and poured into cold water. The hydroxy-quinone was isolated by extracting the precipitate with 2% aqueous sodium acetate, and crystallised from light petroleum (b. p. 100—120°) in yellow needles, m. p. and mixed m. p. with authentic 2-hydroxy-6-methyl-1 : 4-naphthaquinone, 198° (65%).

*Thiele Acetylation of* 6-*Methyl*-1 : 4-*naphthaquinone*.—To a solution of 6-methyl-1 : 4-naphthaquinone (1 g.) in acetic anhydride (8 c.c.) concentrated sulphuric acid (4 drops) was added. After 6 days the colourless needles (m. p. 141°) which had separated were collected. Dilution of the mother-liquor with water gave a precipitate which, after repeated crystallisation from aqueous acetic acid and then from benzene–light petroleum, afforded needles, m. p 139—141° (total yield 69%). (1 : 2 : 4-Triacetoxy-6-methylnaphthalene has m. p. 158°, 1 : 3 : 4-triacetoxy-6-methylnaphthalene has m. p. 161—162°. A mixture of the two has m. p. *ca.* 140°. A mixture of either with the product of m. p. 141° has an intermediate m. p.) The product of m. p. 141° was rapidly hydrolysed by cold aqueous-alcoholic sodium hydroxide, and acidification of the red solution obtained gave, after crystallisation from benzene–light petroleum, clusters of yellow needles, m. p. 177—178° (Found : C, 70·1; H, 4·25. $C_{11}H_8O_3$ requires C, 70·2; H, 4·25%). (2-Hydroxy-6-methyl-1 : 4-naphthaquinone has m. p. 198—199°, 3-hydroxy-6-methyl-1 : 4-naphthaquinone has m. p. 206°. A mixture of the two has m. p. *ca.* 180°. A mixture of either with the product of m. p. 177—178° has an intermediate m. p.). Attempts to separate the material of m. p. 177—178° into two components by fractional crystallisation, extraction with buffer solutions, chromatography on calcium carbonate, etc., were unsuccessful. However, when the product of m. p. 177—178° (1 g.) was refluxed in alcohol (80 c.c.) with aniline (0·5 c.c.) for 24 hr., 2-anilino-6-methyl-1 : 4-naphthaquinone separated on cooling. This was collected and the process repeated, giving in all a 90% yield of the 2 : 6-isomer, but no 3 : 6-isomer could be isolated. It is therefore concluded that the material m. p. 177—178° is a mixture of 2- and 3-hydroxy-6-methyl-1 : 4-naphthaquinones which is largely the 2 : 6-isomer, and that the Thiele acetylation product of m. p. 141° is a mixture of triacetates in which the 1 : 2 : 4 : 6-isomer predominates.

6-*Methyl*-2- *and* -3-p-*tolylthio*-1 : 4-*naphthaquinone*.—A solution of 6-methyl-1 : 4-naphthaquinone (1 g.) and toluene-*p*-thiol (0·6 g.) in methyl alcohol (40 c.c.) was set aside until it became quite dark and then poured on to ice-water (40 c.c.) containing sodium dichromate (1·2 g.) and concentrated sulphuric acid (0·6 c.c.). The precipitate obtained was crystallised several times from light petroleum (b. p. 100—120°), to give two fractions, (*a*) less soluble yellow needles, m. p. 173° (32%), and (*b*) more soluble yellow crystals, m. p. 148° (36%) [Found : (*a*) C, 73·7; H, 5·0; S, 10·7; (*b*) C, 73·9; H, 5·0; S, 10·9. $C_{18}H_{14}O_2S$ requires C, 74·0; H, 4·7; S, 10·8%). Product (*a*) was shown to be 6-*methyl*-3-p-*tolylthio*-1 : 4-*naphthaquinone* as follows : a solution

of toluene-*p*-thiol (0·9 g.) in a little alcohol was neutralised with aqueous sodium hydroxide, brought to the b. p. and added to a hot solution of 3-bromo-6-methyl-1 : 4-naphthaquinone (1·8 g.) in alcohol (100 c.c.). The product obtained on cooling crystallised from light petroleum in yellow needles, m. p. and mixed m. p. with (*a*) 173° (88%). Product (*b*) is presumably the 2-p-*tolylthio*-isomer.

3-*Bromo*-6-*methyl*-1 : 4-*naphthaquinone*.—A solution of 6-methyl-1 : 4-naphthaquinone (1 g.) and bromine (0·9 g.) in glacial acetic acid (20 c.c.) was kept for 10 min. and then poured into ice-water (100 c.c.). The almost colourless precipitate of dibromide (1·5 g.) was collected and added to glacial acetic acid (16 c.c.) containing sodium acetate (0·8 g.). After 5 min.' boiling, water (20 c.c.) was added and the solution filtered (charcoal). The *bromo-quinone* separated on cooling and recrystallised from methyl alcohol in yellow needles, m. p. 103° (78% from the dibromide) (Found : C, 52·45; H, 2·9; Br, 31·6. $C_{11}H_7O_2Br$ requires C, 52·6; H, 2·8; Br, 31·9%).

3-*Chloro*-6-*methyl*-1 : 4-*naphthaquinone*.—A solution of 3-bromo-6-methyl-1 : 4-naphthaquinone (1 g.) in alcohol (30 c.c.) containing concentrated hydrochloric acid (0·5 c.c.) was refluxed for 12 hr., diluted with water, and allowed to cool. The 3-*chloro-quinone* which separated crystallised from aqueous alcohol in yellow crystals, m. p. 91—92° (64%) (Found : C, 63·7; H, 3·3; Cl, 17·3. $C_{11}H_7O_2Cl$ requires C, 63·9; H, 3·4; Cl, 17·15%).

2-*Chloro*-6-*methyl*-1 : 4-*naphthaquinone*.—A mixture of 2-hydroxy-6-methyl-1 : 4-naphthaquinone (0·3 g.) and thionyl chloride (3 c.c.) was refluxed for 12 hr. and excess of thionyl chloride then allowed to evaporate at room temperature. The residual 2-*chloro-quinone* formed yellow crystals, m. p. 149° (52%), from alcohol (Found : C, 63·8; H, 3·25; Cl, 17·35%).

6-*Chloro*-1 : 4-*naphthaquinone*.—Direct oxidation of the chloroprene–benzoquinone Diels–Alder adduct with potassium dichromate and sulphuric acid was found more satisfactory than the step-wise oxidation procedure of Fieser and Brown (*loc. cit.*). Crystallisation from aqueous methyl alcohol yielded yellow crystals, m. p. 109—110° (Fieser and Brown give m. p. 107°).

3-Anilino-6-chloro-1 : 4-naphthaquinone.—A mixture of 6-chloro-1 : 4-naphthaquinone (1 g.), aniline (0·23 c.c.), and alcohol (40 c.c.) was boiled for 1 hr. After being kept at room temperature for several hours, the *anilinoquinone* was collected and crystallised from acetic acid, forming red needles, m. p. 235—236° (84%) (Found : N, 5·15; Cl, 12·3. $C_{16}H_{10}O_2ClN$ requires N, 4·9; Cl, 12·4%).

6-*Chloro*-2- *and* -3-p-*tolylthio*-1 : 4-*naphthaquinone*.—A solution of 6-chloro-1 : 4-naphthaquinone (1 g.) and toluene-*p*-thiol (0·65 g.) in methyl alcohol (25 c.c.) was kept for 15 min. and then oxidised in the usual manner. The product was separated by fractional crystallisation from ethyl alcohol into (*a*) less soluble yellow crystals, m. p. 170° (from glacial acetic acid) (49%), and (*b*) more soluble yellow crystals, m. p. 130° (from methyl alcohol) (36%) [Found : (*a*) Cl, 11·5; S, 10·15; (*b*) Cl, 11·1; S, 10·4. $C_{17}H_{11}O_2ClS$ requires Cl, 11·3; S, 10·2%].

6-*Chloro*-3-*hydroxy*-1 : 4-*naphthaquinone*.—3-Anilino-6-chloro-1 : 4-naphthaquinone was hydrolysed by boiling 50% (v/v) sulphuric acid for 5 min. Crystallisation from methyl alcohol gave yellow crystals, m. p. 204° (Fieser and Brown, *loc. cit.*, give m. p. 205—207°). Reductive acetylation yielded 1 : 3 : 4-triacetoxy-6-chloronaphthalene, m. p. and mixed m. p. 149—150°.

3-*Bromo*-6-*chloro*-1 : 4-*naphthaquinone*.—6-Chloro-1 : 4-naphthaquinone (1 g.) in glacial acetic acid (28 c.c.) was treated with bromine (0·8 g.). After 10 min. the solution was diluted with water, and the dibromide (97%; m. p. 122—126°) collected. The *bromochloroquinone* was obtained by boiling the dibromide with sodium acetate in glacial acetic acid for a few minutes. It crystallised from alcohol in yellow needles, m. p. 175° (81% from dibromide) (Found : C, 43·95; H, 1·5; Hal, 41·4. $C_{10}H_4O_2BrCl$ requires C, 44·2; H, 1·5; Hal, 42·5%).

3 : 6-*Dichloro*-1 : 4-*naphthaquinone*.—(*a*) A solution of 3-bromo-6-chloro-1 : 4-naphthaquinone (0·5 g.) in alcohol (40 c.c.) containing concentrated hydrochloric acid (2 c.c.) was refluxed for 30 min. and filtered (charcoal). The *dichloro-quinone* separated in yellow plates, m. p. 188—189° (88%). (*b*) 6-Chloro-3-hydroxy-1 : 4-naphthaquinone (0·5 g.) and thionyl chloride (5 c.c.) were heated under reflux overnight. After evaporation of the excess of thionyl chloride, the residue was taken up in ether, extracted with 2% aqueous sodium acetate, and dried, and the solvent was removed. The residue crystallised from alcohol in yellow plates, m. p. 188—189° (Found : C, 52·6; H, 1·8; Cl, 31·0. $C_{10}H_4O_2Cl_2$ requires C, 52·9; H, 1·8; Cl, 31·3%).

1 : 2 : 4- *and* 1 : 3 : 4-*Triacetoxy*-6-*chloronaphthalene*.—The results of Thiele acetylation of 6-chloro-1 : 4-naphthaquinone were substantially the same as recorded by Fieser and Brown (*loc. cit.*). We obtained (*a*) 1 : 2 : 4-triacetoxy-6-chloronaphthalene, m. p. 163—164° (36%), more soluble in methyl alcohol than (*b*) 1 : 3 : 4-triacetoxy-6-chloronaphthalene, m. p. 149—150°

(49%) (Fieser and Brown give m. p. 143—144°. These authors have confused the m. p.s of the two isomers).

6-*Acetamido*-1 : 4-*naphthaquinone*.—This was prepared by the procedure of Fierz-David, Blangey, and Krannichfeldt (*Helv. Chim. Acta*, 1947, **30**, 831) using the mixture of 6- and 7-acetamido-1-naphthols obtained by sulphonation of β-naphthylamine followed by potash fusion and acetylation (yield 70%).

6-*Acetamido*-2-*anilino*-1 : 4-*naphthaquinone*.—(*a*) 6-Acetamido-1 : 4-naphthaquinone (0·5 g.) and aniline (0·25 c.c.) were refluxed in alcohol (50 c.c.) for 10 hr. and then set aside. The *anilinoquinone* separated overnight and recrystallised from alcohol as red needles, m. p. 330° (89%). (*b*) 6-Acetamido-2-bromo-1 : 4-naphthaquinone (0·5 g.) and aniline (0·25 c.c.) were refluxed in alcohol for 10 hr. Red needles, m. p. 328° (76%), separated on cooling, identical with those obtained as above (Found : C, 70·2; H, 4·5; N, 8·8. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·15%).

6-*Acetamido*-2- *and* -3-p-*tolylthio*-1 : 4-*naphthaquinone*.—A mixture of 6-acetamido-1 : 4-naphthaquinone (1 g.) and toluene-*p*-thiol (0·3 g.) in methyl alcohol (50 c.c.) was heated to the b. p. and then kept at room temperature for several hours. Small yellow needles, m. p. 244—245° (0·2 g.), separated. Oxidation of the mother-liquor with sodium dichromate and sulphuric acid at room temperature gave a product which was separated into two fractions by crystallisation from glacial acetic acid : (*a*) a *tolylthio*-compound as yellow needles, m. p. 255° (decomp. from 230°) (42%) (from methyl alcohol), less soluble than (*b*) its *isomer*, orange crystals, m. p. 220° (31%) (from aqueous acetic acid). Recrystallisation of the first crop gave (*a*) [Found : (*a*) N, 4·3; S, 9·6; (*b*) N, 3·9; S, 9·3. $C_{19}H_{15}O_3NS$ requires N, 4·15; S, 9·5%]. Product (*a*) was also obtained as follows: toluene-*p*-thiol (0·2 g.) in a little alcohol was neutralised with aqueous sodium hydroxide, and the solution brought to the boil and added to a hot solution of 6-acetamido-2-bromo-1 : 4-naphthaquinone in alcohol (50 c.c.). On cooling, yellow needles, m. p. 252—254°, separated : mixed m. p. with material (*a*), 254—255°.

6-*Acetamido*-3-*bromo*-1 : 4-*naphthaquinone*.—(*a*) 6-Acetamido-1 : 4-naphthaquinone (0·4 g.) and bromine (0·32 g.) were dissolved in glacial acetic acid (50 c.c.). After 15 min. the solution was poured into water (300 c.c.) from which the *bromo-quinone* gradually separated. It crystallised from alcohol in orange crystals, m. p. 237° (67%). (*b*) 7-Acetamido-2 : 4-dibromo-1-naphthol (1 g.) in glacial acetic acid (50 c.c.) was oxidised by the addition of chromium trioxide (1 g.) in water (3 c.c.). After 15 min. the solution was diluted with water, and the precipitate was crystallised from alcohol in orange crystals, m. p. 237° (73%), identical with the above product (Found : N, 4·5; Br, 27·0. $C_{12}H_8O_3NBr$ requires N, 4·7; Br, 27·2%).

6-*Acetamido*-2-*bromo*-1 : 4-*naphthaquinone*.—6-Acetamido-2 : 4-dibromo-1-naphthol was oxidised with chromic acid as before. The *quinone* separated from alcohol in orange crystals, m. p. 241° (82%) (Found : N, 4·4; Br, 27·0. $C_{12}H_8O_3NBr$ requires N, 4·7; Br, 27·2%).

6-*Acetamido*-2 : 4-*dibromo*-1-*naphthol*.—6-Acetamido-1-naphthol (1·6 g.) in glacial acetic acid (20 c.c.) was treated with bromine (3 g.). A precipitate appeared immediately and was collected after 30 min. and crystallised from chlorobenzene, to yield plates, m. p. 205—207° (decomp. from 187°) (86%) (Found : N, 3·85; Br, 44·2. $C_{12}H_9O_2NBr_2$ requires N, 3·9; Br, 44·5%). The *acetate* was obtained in needles, m. p. 225° (from aqueous methanol) (Found : N, 3·3; Br, 39·6. $C_{14}H_{11}O_3NBr_2$ requires N, 3·5; Br, 39·9%).

7-*Acetamido*-2 : 4-*dibromo*-1-*naphthol*.—This *isomer* was prepared by the foregoing procedure from 7-acetamido-1-naphthol. It separated from chlorobenzene in needles, m. p. 212° (decomp. from 200°) (80%) (Found : N, 3·75; Br, 44·3%). The *acetate* crystallised from acetic acid in needles, m. p. 210° (decomp. from 196°) (Found : N, 3·7; Br, 40·2%).

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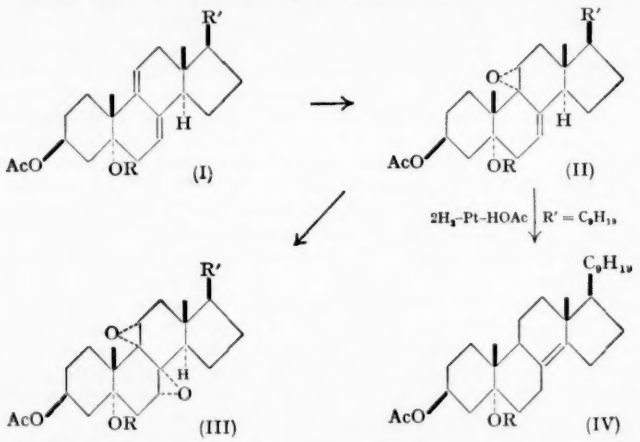
## 583. *Studies in the Steroid Group. Part LXI.* Oxidation of 5α-Hydroxy- and 5α-Acetoxy-Δ$^{7:9}$-steroids.*

By Peter Bladon, H. B. Henbest, E. R. H. Jones, Geoffrey W. Wood, and (in part) D. C. Eaton and A. A. Wagland.

Peracid oxidation of 7 : 9-dienes of the above type results first in the formation of 9α : 11α-epoxides. Further oxidation then leads to either 7 : 8-9 : 11-diepoxides or to 7-keto-9 : 11-epoxides; the latter are converted into 11α-hydroxy-7-keto-5 : 8(9)-dienes on treatment with alkali. The unreactivity of the Δ$^{7}$-bond in 3 : 5-diacetoxy-9α : 11α-epoxy-Δ$^{7:22}$-steroids permits selective ozonolysis of the side-chain double bond.

In earlier papers in this series (Parts LVI and LVII; *J.*, 1952, 4883, 4890) methods of preparing 5α-hydroxy- and 5α-acetoxy-Δ$^{7:9}$-steroids (I) were discussed, the presence of the substituents at the 5-position being thought to be of considerable value for the eventual formation of 3-keto-Δ$^{4}$-steroids. After a study of the oxidation of such dienes had been commenced with a view to the introduction of an 11-oxygen function, several reports have appearedd escribing the peracid oxidation of ergosterol-D, the 5-hydrogen analogue of our compounds, the most important observation being the formation of a monoepoxide by means of perbenzoic or monoperphthalic acid (cf. Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106).




Treatment of the 5α-hydroxy-7 : 9-dienes (I; R = H) containing $C_9H_{19}$, CMe:CH·OAc, and COMe side chains with 1 mol. of monoperphthalic acid afforded the corresponding 9α : 11α-epoxides (II; R = H), the structures of the products being confirmed by their further reactions (see following paper). Better yields of 9α : 11α-epoxides were obtained by starting with 5α-acetoxy-7 : 9-dienes (3 : 5-diacetoxy-compounds) (I; R = Ac), the 5-acetate group not hindering the approach of peracid to the 9 : 11-bond. Conversion of the diacetate–epoxide (II; R = Ac, R′ = $C_9H_{19}$) into the 5-hydroxy-epoxide (II; R = H, R′ = $C_9H_{19}$), by hydrolysis of both acetate groups followed by mild acetylation, proved that similar epoxides were being formed in both series. Hydrogenation of these monoepoxides with R′ = $C_9H_{19}$ took place with platinum and acetic acid, but the products were 5α-hydroxy-Δ$^{8(14)}$-compounds (IV; R = H and Ac). Further oxidation of the 5-hydroxy-epoxide (II; R = H, R′ = $C_9H_{19}$) with monoperphthalic acid gave an excellent yield of the diepoxide (III; R = H, R′ = $C_9H_{19}$), whereas the corresponding 5-acetate

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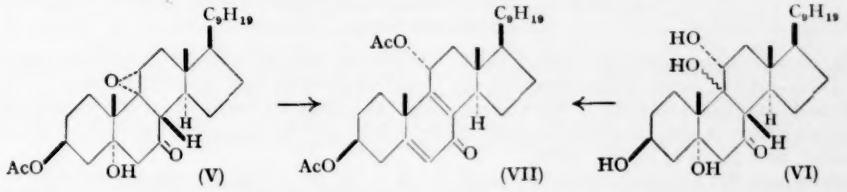
was mostly recovered unchanged under the same conditions. The steric hindrance apparently imposed by the α-orientated 5-acetoxy-group in this last reaction suggests that 7 : 8-epoxide formation in the 5-hydroxyl series takes place by rearwise approach of peracid, and thus a 7α : 8α-epoxy-configuration can be assigned provisionally.

The reaction of performic acid with 7 : 9-dienes (R′ = $C_9H_{19}$) has also been studied. Stirring the two-phase mixture of the steroid in chloroform and excess of aqueous performic acid afforded somewhat similar results to those described above, the 5-hydroxy-compound yielding the same 7 : 8-9 : 11-diepoxide, and the 5-acetate the same 9 : 11-monoepoxide, together, however, with some of the 5-acetate diepoxide (III; R = Ac, R′ = $C_9H_{19}$), the structure of which was confirmed by complete hydrolysis followed by mild acetylation to (III; R = H, R′ = $C_9H_{19}$), identical with that prepared in the 5-hydroxy-series. On the other hand, when the performic acid reaction with (I; R = H, R′ = $C_9H_{19}$) was conducted in homogeneous solution (addition of dioxan), a 7-keto-9α : 11α-epoxide (V) could be isolated by crystallization from methanol in about 25% yield [the same keto-



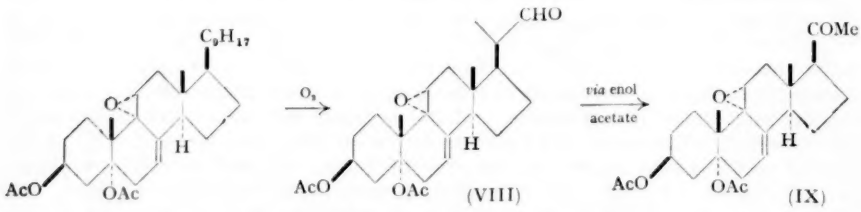

oxide was formed in small amount together with the 9 : 11-epoxide and some 7 : 8-9 : 11-diepoxide when (I; R = H, R′ = $C_9H_{19}$) was treated with 1·4 mols. of monoperphthalic acid in ether]. (In the 5-acetate series, " homogeneous " performic acid gave a mixture which could not be separated by chromatography on alumina owing to changes occurring on the column.) Another product of the reaction with the 5-hydroxy-compounds appeared to be the 3-acetate 9(or 11)-formate of the tetrol (VI), for treatment of the methanolic mother-liquor (after the crystallization of V) with dilute hydrochloric acid caused separation of the rather insoluble tetrol itself in about 40% yield. Acetylation of (VI) under mild conditions afforded a 3 : 11-diacetate, indicating an α-configuration for the 11-hydroxyl group—the 9-hydroxyl group should be β-orientated according to the method of formation, but this is as yet without experimental confirmation.

The formation of a 7-keto-9α : 11α-epoxide by the reaction of performic acid with a 5-unsubstituted 7 : 9-diene is the key step in the method first described by Stork, Romo, Rosenkranz, and Djerassi (*J. Amer. Chem. Soc.*, 1951, **73**, 3546) for the introduction of an 11-oxygen substituent. These authors describe the ready isomerization of such epoxy-ketones into 11α-hydroxy-7-keto-$\Delta^{8(9)}$-steroids under alkaline conditions. Similar alkaline treatment of the 5-hydroxy-compound (V) or the tetrol (VI) gave (after acetylation) the doubly unsaturated ketone (VII) with loss of the 5-hydroxyl group. Again, the ready acetylation of the 11-hydroxyl group leading to (VII) provides confirmation of the α-orientation of the original 9 : 11-epoxide group.

The formation of different major products from (I) by using performic acid in homogeneous or " two-phase " reaction conditions is probably related to the different acidities of the media in which the steroid is dissolved. It is believed that in both cases a 9 : 11-monoepoxide is first produced which, in the two-phase method is transformed into the diepoxide by the low concentration of performic acid in the chloroform layer. In the homogeneous solution (with a relatively high concentration of formic and performic acids), the 9 : 11-monoepoxide undergoes isomerization (*via* a $\Delta^{8(9)}$-7 : 11-diol) into a 7-keto-$\Delta^{9(11)}$-steroid which is then epoxidized or hydroxylated to give (V) or (VI).

The lack of reactivity of the 7 : 8-bond in the 3 : 5-diacetates (II; R = Ac) towards peracids paralleled that of 9 : 11-double bonds in compounds containing a 5 : 8-epidioxy-bridge (cf. Part LVIII, *J.*, 1952, 4894). It was shown in Part LVII (*loc. cit.*) that a compound of the latter type, 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene, could be ozonized selectively at the side-chain double bond. When the same ozonolysis technique is used,

controlled oxidation of (II; R = Ac, R′ = $C_9H_{17}$, following paper) yields the aldehyde (VIII). The enol acetate of (VIII) was identical with that prepared by the action of mono-




perphthalic acid on the corresponding 7 : 9-diene (see above); on further selective ozonolysis it afforded the 20-ketone (IX).

## Experimental

M. p.s were determined on a Kofler block. Rotations were measured in chloroform solution in a 1-dm. tube at room temperature (18—25°), and ultra-violet light absorption measurements were made in ethanol solution. Peter Spence alumina (Grade H) was used for chromatography; when necessary it was deactivated with dilute acetic acid as described by Farrar, Hamlet, Henbest, and Jones (*J.*, 1952, 2657).

3β-*Acetoxy*-9α : 11α-*epoxyergost*-7-*en*-5α-*ol* (II; R = H, R′ = $C_9H_{19}$).—Monoperphthalic acid (1·4 mols.), dissolved in dry ether (50 c.c.), was added to a solution of 3β-acetoxyergosta-7 : 9-dien-5α-ol (1·75 g.) in dry ether (200 c.c.). After 24 hr. at 0° and 48 hr. at 25°, the mixture was diluted with ether and washed with dilute alkali, water, and ferrous sulphate solution, dried, and evaporated to dryness under reduced pressure. The residue was dissolved in light petroleum–benzene (1 : 1) and introduced on to a column of deactivated alumina (200 g.). Elution with benzene (1·1 l.) gave, after recrystallisation from *iso*propyl ether, 3β-acetoxy-7α : 8α-9α : 11α-diepoxyergostan-5α-ol (330 mg.) as fine needles, m. p. and mixed m. p. with an authentic sample (see below) 221—226°, $[\alpha]_D$ +3° (*c*, 0·91). Further elution with benzene (1·2 l.) afforded 3β-*acetoxy*-9α : 11α-*epoxyergost*-7-*en*-5α-*ol* (450 mg.), crystallizing from methanol as plates, m. p. 222—227°, $[\alpha]_D$ +15° (*c*, 0·74) (Found: C, 75·95; H, 10·15. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). Elution with benzene–ether (19 : 1) (600 c.c.) gave, after crystallization from methanol, 3β-acetoxy-9α : 11α-epoxyergostan-7-one (120 mg.), m. p. and mixed m. p. with an authentic sample (see below), 184·5—186°, $[\alpha]_D$ −44° (*c*, 0·65).

This experiment shows the nature of the products obtained by using considerably more than 1 mol. of peracid. When 1—1·1 mols. of peracid were used, the 9 : 11-epoxide could be isolated by crystallization of the product from methanol, in 50% yield.

Hydrolysis of 3β-acetoxy-9α : 11α-epoxyergost-7-en-5α-ol with warm 5% methanolic potassium hydroxide yielded the corresponding 3β : 5α-*diol*, crystallizing from *iso*propyl ether–methanol (1 : 1) as blades, m. p. 214·5—219·5°, $[\alpha]_D$ −6° (*c*, 0·69) (Found: C, 78·35; H, 10·6. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·75%).

3β-*Acetoxy*-7α : 8α-9α : 11α-*diepoxyergostan*-5α-*ol* (III; R = H, R′ = $C_9H_{19}$).—(*a*) Solutions of (i) 3β-acetoxyergosta-7 : 9-dien-5α-ol (5 g.) in chloroform (100 c.c.) and (ii) 100-vol. hydrogen peroxide (25 c.c.) in 95% formic acid (25 c.c.) were stirred together for 16 hr. at 20°. Formic acid was removed from the chloroform layer by washing with alkali, and the solvent was then removed under reduced pressure. Crystallization from methanol afforded the *diepoxide* (2 g.), m. p. 224—226°, $[\alpha]_D$ +3° (*c*, 1·0) (Found: C, 73·6; H, 9·9. $C_{30}H_{48}O_5$ requires C, 73·75; H, 9·9%).

Alkaline hydrolysis gave the 3β : 5α-*diol*, crystallizing from methanol as needles, m. p. 253—256°, $[\alpha]_D$ −1° (*c*, 1·0) (Found: C, 73·3; H, 10·6. $C_{28}H_{46}O_4,CH_3{\cdot}OH$ requires C, 72·75; H, 10·55%).

(*b*) Monoperphthalic acid (2 mols.) in dry ether (20 c.c.) was added to a solution of 3β-acetoxy-9α : 11α-epoxyergost-7-en-5α-ol (200 mg.) in dry ether (20 c.c.). The mixture was kept at 0° for 24 hr. and then at 25° for 72 hr., after which it was washed with dilute alkali, dried, and evaporated. Chromatography on deactivated alumina (25 g.) gave the diepoxide (130 mg.), m. p. and mixed m. p. 222—227°, $[\alpha]_D$ +2° (*c*, 0·98), and also some starting material (50 mg.).

3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergost*-7-*ene* (II; R = Ac, R′ = $C_9H_{19}$).—Monoperphthalic

acid (1·1 mols.) in ether (30 c.c.) was added to a solution of 3β : 5α-diacetoxyergosta-7 : 9-diene (3·1 g.) in dry ether (25 c.c.). The reaction was allowed to proceed, and the mixture was then worked up as described above for the 5-hydroxy-compound. Crystallization of the total product from methanol gave the 9 : 11-*epoxide* (2 g.) as needles, m. p. 144·5—147·5°, $[\alpha]_D$ +71° (*c*, 0·86) (Found : C, 74·95; H, 9·95. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%). When this epoxide (200 mg.) was treated with an excess of monoperphthalic acid at 20° for 2 days, 180 mg. of pure starting material were recovered after chromatography.

3β : 5α-*Diacetoxy*-7α : 8α-9α : 11α-*diepoxyergostane* (III; R = Ac, R′ = $C_9H_{19}$).—Solutions of 3β : 5α-diacetoxyergosta-7 : 9-diene (1·5 g.) in chloroform (30 c.c.) and of 30% hydrogen peroxide (7·5 c.c.) in 98% formic acid (7·5 c.c.) were stirred together at 20° for 18 hr. The steroid was isolated with chloroform, and the gummy product chromatographed in benzene on deactivated alumina (75 g.). Light petroleum–benzene (3 : 1) eluted the 9α : 11α-monoepoxide (350 mg.), m. p. and mixed m. p. with the product from the previous experiment, 145—147°, $[\alpha]_D$ +66° (*c*, 0·4). Elution with light petroleum–benzene (1 : 1) afforded the 7α : 8α-9α : 11α-*diepoxide* (300 mg.), crystallizing from methanol as needles, m. p. 178—179°, $[\alpha]_D$ +22° (*c*, 0·5) (Found : C, 72·3; H, 9·6. $C_{32}H_{50}O_6$ requires C, 72·5; H, 9·45%).

*Hydrolysis of* 5α-*Acetoxy-epoxides*.—A solution of lithium aluminium hydride (4 mols.) in ether was added to 3β : 5α-diacetoxy-9α : 11α-epoxyergost-7-ene (400 mg.) in ether (10 c.c.) at −70°. The mixture was allowed to warm to 20°, and the excess of hydride decomposed with ethyl acetate. Isolation with ether, followed by crystallization of the product from *iso*propyl ether–methanol (1 : 1), gave the 3 : 5-diol, m. p. and mixed m. p. (see above) 215—220°, $[\alpha]_D$ −4° (*c*, 0·78). Mild acetylation gave the 3-acetate, m. p. and mixed m. p. (see above) 221—226°.

Similar treatment of 3β : 5α-diacetoxy-7α : 8α-9α : 11α-diepoxyergostane afforded (after mild acetylation) 3β-acetoxy-7α : 8α-9α : 11α-diepoxyergostan-5α-ol, m. p. and mixed m. p. 217—223°, $[\alpha]_D$ 0° (*c*, 0·4), identical with the product described above.

*Hydrogenation of* 9α : 11α-*Epoxy*-$\Delta^7$-*compounds*.—3β-Acetoxy-9α : 11α-epoxyergost-7-en-5α-ol (200 mg.) in acetic acid (25 c.c.) was shaken with hydrogen and prereduced Adams catalyst (50 mg.) for 10 hr., 2·1 mols. being taken up. Filtration, evaporation under reduced pressure, and crystallization of the product from methanol gave 3β-acetoxyergost-8(14)-en-5α-ol (IV; R = H) as needles, m. p. and mixed m. p. 156—158°, $[\alpha]_D$ −3° (*c*, 1·3).

Similar reduction of the corresponding 3 : 5-diacetate afforded 3β : 5α-diacetoxyergost-8(14)-ene (IV; R = Ac), m. p. and mixed m. p. 98—104°, $[\alpha]_D$ +20° (*c*, 1·34).

3β : 22-*Diacetoxybisnorchola*-7 : 9 : 20(22)-*trien*-5α-*ol and its Acetylation to* (I; R = Ac, R′ = CMe:CH·OAc).—3β : 22-Diacetoxy-5α : 8α-epidioxybisnorchola-9 : 20(22)-diene (2 g.) in boiling acetic acid (25 c.c.) was treated with zinc dust (2 g.) in small portions. The mixture was cooled and filtered and the product isolated with chloroform. Crystallization from methanol gave the 5α-*hydroxy*-compound (1·3 g.), m. p. 162—165°, $[\alpha]_D$ +31° (*c*, 0·97) (Found : C, 72·85; H, 8·6. $C_{26}H_{36}O_5$ requires C, 72·9; H, 8·45%). Ultra-violet absorption : Max. 2360 and 2420 Å; ε = 20,600 and 20,700. Infra-red spectrum (in Nujol) : peaks at 3750 (hydroxyl), 1750, 1215 (enol acetate), 1730, 1250 (acetate), and 1657 cm.$^{-1}$ ($\Delta^7$, $\Delta^9$, $\Delta^{20(22)}$).

Acetylation was achieved by heating under reflux for 24 hr. a solution of the compound (1·3 g.) in chloroform (15 c.c.), pure acetyl chloride (13 c.c.), and dimethylaniline (17 c.c.). The steroid was isolated with ether; crystallization from methanol afforded 3β : 5α : 22-*triacetoxy-bisnorchola*-7 : 9 : 20(22)-*triene* (1·1 g.), m. p. 171—175°, $[\alpha]_D$ +101° (*c*, 0·93) (Found : C, 71·1; H, 8·25. $C_{28}H_{38}O_6$ requires C, 71·45; H, 8·15%). Ultra-violet absorption : Max. 2350 and 2420 Å; ε = 22,300 and 22,200. Infra-red spectrum (in Nujol) : peaks at 1747, 1225 (enol acetate), 1738, 1722, and 1250 cm.$^{-1}$ (acetate).

3β : 5α : 22-*Triacetoxy*-9α : 11α-*epoxybisnorchola*-7 : 20(22)-*diene* (II; R = Ac, R′ = CMe:CH·OAc).—Treatment of the foregoing triacetoxy-triene with monoperphthalic acid (1·1 mols.) in ether at 20° for 36 hr. gave a good yield of the 9α : 11α-*epoxide* (needles from methanol), m. p. 184—186°, $[\alpha]_D$ +47° (*c*, 1·1) (Found : C, 69·05; H, 7·7. $C_{28}H_{38}O_7$ requires C, 69·1; H, 7·9%). Infra-red spectrum (in Nujol) : peaks at 1740, 1205 (enol acetate), 1720, 1250 (acetate), and 1665 cm.$^{-1}$ ($\Delta^7$, $\Delta^{20(22)}$). When the reaction was allowed to proceed for insufficient time a molecular *complex* of the 9 : 11-epoxide and the starting material crystallized (as needles from methanol), m. p. 165—166°, $[\alpha]_D$ +69° (calc., +74°) (Found : C, 70·25; H, 8·1. $C_{28}H_{38}O_7$,$C_{28}H_{38}O_6$ requires C, 70·3; H, 8·0%).

3β-*Acetoxy*-9α : 11α-*epoxy*-5α-*hydroxy*allo*pregn*-7-*en*-20-*one* (II; R = H, R′ = COMe).—3β-Acetoxy-5α-hydroxy*allo*pregna-7 : 9-dien-20-one (200 mg.), dissolved in dioxan (3 c.c.) and ether (3 c.c.), was treated with monoperphthalic acid (1·1 mols.) in ether. The mixture was

kept at 0° for 24 hr. and at 20° for 12 hr.; then the steroid was isolated with ether. Crystallization from methanol afforded a good yield of the 9α : 11α-*epoxide* as needles, m. p. 223—228°, $[\alpha]_D$ +48° (*c*, 0·5) (Found : C, 71·2; H, 8·6. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

3β-*Acetoxy*-9α : 11α-*epoxy*-5α-*hydroxyergostan*-7-*one* (V) and 3β : 5α-9ξ : 11α-*tetrahydroxyergostan*-7-*one* (VI).—Dioxan (300 c.c.) was added to a mixture of 3β-acetoxyergosta-7 : 9-dien-5α-ol (11·3 g.) dissolved in chloroform (200 c.c.), 100-vol. hydrogen peroxide (60 c.c.), and formic acid (60 c.c.), and the resultant homogeneous solution was kept at 20° overnight. The steroid was isolated with chloroform and, after removal of solvent, the product was dissolved in methanol (50 c.c.) and kept at 0° for 2 days. The product (m. p. 175—185°) which separated was recrystallized from methanol, to give the 9 : 11-*epoxy*-7-*ketone* (1·8 g.), m. p. 187—190°, $[\alpha]_D$ −45° (*c*, 1·45) (Found : C, 73·8; H, 9·95. $C_{30}H_{48}O_5$ requires C, 73·75; H, 9·9%). Infra-red spectrum (in Nujol) : peaks at 3450 (hydroxyl), 1720 (acetate and keto-groups), 1245 cm.$^{-1}$ (acetate).

The pale yellow mother-liquors were treated with a few drops of concentrated hydrochloric acid. After 3 days at 20°, the solution was concentrated to a small bulk under reduced pressure, and the solid (3·4 g.), m. p. 230—240°, filtered off. A portion was recrystallized from chloroform methanol and from ethanol, to give the *tetrahydroxy*-7-*ketone* as plates, m. p. 240—245° (decomp.), $[\alpha]_D$ −27° (*c*, 1·075 in pyridine) (Found : C, 72·5; H, 10·25. $C_{28}H_{48}O_5$ requires C, 72·35; H, 10·4%). Infra-red spectrum (in Nujol) : peaks at 3550, 3510, 3290 (hydroxyl groups), 1718 (7-keto-group), but no peak at 1245 cm.$^{-1}$ (acetate absent).

Acetic anhydride and pyridine at 20° converted the tetrol into 3β : 11α-*diacetoxy*-5α : 9ξ-*dihydroxyergostan*-7-*one*, crystallizing from ethyl acetate as needles, m. p. 243—245°, $[\alpha]_D$ −29° (*c*, 1·37) (Found : C, 69·95; H, 9·4. $C_{32}H_{52}O_7$ requires C, 70·05; H, 9·55%).

3β : 11α-*Diacetoxyergosta*-5 : 8(9)-*dien*-7-*one* (VII).—(*a*) A solution of 3β-acetoxy-9α : 11α-epoxy-5α-hydroxyergostan-7-one (255 mg.) and potassium hydroxide (3 g.) in methanol (30 c.c.) was kept at 20° for 16 hr. The steroid was isolated with ether and reacetylated with acetic anhydride and pyridine. Crystallization from methanol afforded a 60% yield of the *diacetate* as needles, m. p. 203—205°, $[\alpha]_D$ +75° (*c*, 1·04) (Found : C, 74·7; H, 9·55. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Ultra-violet absorption : Max. 2520 and 3320 Å; ε = 13,500 and 40 respectively. Infra-red spectrum (in Nujol) : peaks at 1721, 1240 (acetate), 1660 (7-ketone), 1620 ($\Delta^5$), and 1604 cm.$^{-1}$ ($\Delta^{8(9)}$); no hydroxyl bands.

(*b*) A solution of 3β : 11α-diacetoxy-5α : 9-dihydroxyergostan-7-one (50 mg.) and potassium hydroxide (200 mg.) in methanol (2 c.c.) and dioxan (2 c.c.) was kept at 20° for 70 hr. Isolation with ether and methylation as in (*a*) gave a product which crystallized from methanol as needles, m. p. and mixed m. p. 202—204°, $[\alpha]_D$ +68° (*c*, 0·5).

3β : 5α-*Diacetoxy*-9α : 11α-*epoxybisnorchol*-7-*en*-22-*al* (VIII).—A solution of 3β : 5α-diacetoxy-9α : 11α-epoxyergosta-7 : 22-diene (9·3 g.) in ethyl acetate (250 c.c.) at −70° was treated with 1·1 mols. of ozone dissolved in ethyl acetate at −70°. Nitrogen was bubbled through while the solution was allowed to reach 20°, then the ozonide was decomposed by shaking the solution with aqueous ferrous sulphate and washed with water and 2% aqueous sodium hydroxide to remove acidic materials. After being dried ($CaCl_2$) the ethyl acetate was evaporated under reduced pressure. The residual gum in benzene was chromatographed on deactivated alumina (200 g.). Light petroleum–benzene (2 : 1) eluted a gum, but elution with benzene yielded the *aldehyde* (1·8 g.) (crystallized from *iso*propyl ether), m. p. 166—173°, $[\alpha]_D$ +63° (*c*, 2·06) (Found : C, 69·95; H, 8·35. $C_{26}H_{36}O_6$ requires C, 70·05; H, 8·2%). Infra-red spectrum (in Nujol) : peaks at 2700 (aldehyde C−H stretching), 1735 and 1250 (acetate), and 1721 cm.$^{-1}$ (aldehyde).

3β : 5α : 22-*Triacetoxy*-9α : 11α-*epoxybisnorchola*-7 : 20(22)-*diene* (II; R = Ac, R′ = $CMe{:}CH{\cdot}OAc$).—The foregoing aldehyde (1·74 g.), redistilled acetic anhydride (6 c.c.), and fused potassium acetate (0·39 g.) were heated in an oil-bath at 120—130° for 6 hr. The product was extracted with benzene and, after removal of solvents under reduced pressure, was redissolved in benzene and introduced on to deactivated alumina (100 g.). Elution with benzene yielded the enol acetate, which on crystallization from methanol gave needles (0·91 g.), m. p. 180—185°, $[\alpha]_D$ +44° (*c*, 0·4) (Found : C, 68·95; H, 8·05. Calc. for $C_{28}H_{38}O_7$ : C, 69·1; H, 7·9%). The infra-red spectrum was identical with that of the previous material (see above).

3β : 5α-*Diacetoxy*-9α : 11α-*epoxy*allo*pregn*-7-*en*-20-*one* (IX).—The enol acetate (0·9 g.) in ethyl acetate (25 c.c.) was ozonized at −70° as described for the preparation of the aldehyde. The material was purified by elution through deactivated alumina (75 g.) with benzene, the *ketone* (0·3 g.) being obtained. Crystallization from methanol gave needles, m. p. 160—169°, $[\alpha]_D$ +52° (*c*, 0·9) (Found : C, 69·65; H, 8·25. $C_{25}H_{34}O_6$ requires C, 69·75; H, 7·95%). Infra-red spectrum (in Nujol) : peaks at 1735, 1730, 1250 (acetate), and 1715 cm.$^{-1}$ (20-ketone).

Thanks are offered to Glaxo Laboratories Ltd. for financial assistance (to P. B.) and for gifts of materials. One of the authors (G. W. W.) thanks the Department of Scientific and Industrial Research for a maintenance grant. The infra-red spectra were determined under the direction of Dr. G. D. Meakins, and the microanalyses are by Messrs. E. S. Morton and H. Swift.

THE UNIVERSITY, MANCHESTER, 13. [*Received, April 11th,* 1953.]

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## 584. (*a*) *Studies in the Steroid Group. Part LXII.** (*b*) *Studies in the Synthesis of Cortisone. Part I.*

### *A Novel Route to* 11-*Ketosteroids.*

By (*a*) PETER BLADON, H. B. HENBEST, E. R. H. JONES, (MISS) B. J. LOVELL, GEOFFREY W. WOOD, and GILBERT F. WOODS, and (*b*) J. ELKS, R. M. EVANS, D. E. HATHWAY, J. F. OUGHTON, and G. H. THOMAS.

It has been shown that 11-keto-$\Delta^7$-9β-steroids (II) are the initial products of isomerising 9α : 11α-epoxy-$\Delta^7$-compounds (I) in the *allo*steroid series with the boron trifluoride–ether complex. These new unsaturated ketones are isolated in good yields and can be isomerised successively to 11-keto-$\Delta^7$-9α-compounds and 11-keto-$\Delta^{8(9)}$-steroids. The unconjugated 7 : 8-bond in the 11-keto-$\Delta^7$-9β-steroids, in contrast to that in the 9α-compounds, can be hydrogenated, and the resulting 11-keto-9β-compounds (III) can be isomerised by alkali to 11-ketones of natural (9α-)configuration (IV). These sequences of reactions have been carried out with compounds containing hydrogen, or a hydroxy- or acetoxy-substituent, at $C_{(3)}$ and having the ergostane, pregnane, or bisnorcholanic acid side-chain, and have led to a new synthesis of 11-ketoprogesterone. Some hydrogenation experiments with 11-keto-$\Delta^7$-9α- and 11-keto-$\Delta^{8(9)}$-steroids are also described. Mention is made of the stereochemical implications of abnormal configuration at the 8 : 9-bridgehead, with particular reference to the structure of the 11-keto-stanol obtained by palladium-catalysed hydrogenation of 3β-acetoxyergosta-8(9) : 22-dien-11-one.

ONE of the most direct methods for introducing an 11-keto-group into the readily available steroids containing a 7 : 9-diene system is that first described by Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2106; cf. Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696; and Sondheimer, Yashin, Rosenkranz, and Djerassi, *ibid.*, p. 2696). The first group of authors showed that small amounts of boron trifluoride–ether complex in benzene solution converted 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (I; R = H, R′ = $C_9H_{17}$) into the isomeric 11-keto-$\Delta^{8(9)}$-compound (VI; R = H, R′ = $C_9H_{17}$). One of the first of our present observations was that the yield of unsaturated ketone from this reaction could be improved by using 1 mol. of boron trifluoride–ether complex and a shorter reaction time. A more detailed investigation of this isomerisation reaction led to the discovery that a βγ-unsaturated ketone was an intermediate in the rearrangement, the first evidence for this being obtained by two different methods.

The course of the reaction in benzene could be followed polarimetrically, and it was then observed that the rotation dropped rapidly from that of the epoxide ($[\alpha]_D$ −40°) to a minimum ($[\alpha]_D$ about −170°) and then increased more slowly to a constant value of approximately $[\alpha]_D$ +90°, corresponding to complete formation of the conjugated ketone (VI; R = H, R′ = $C_9H_{17}$). If the mixture was worked up when the rotation was at the most negative value, a new ketone, shown to be (II; R = H, R′ = $C_9H_{17}$), could be isolated in excellent yield. The other approach involved the substitution of ether for benzene as solvent; rearrangement was then very much slower, but the new βγ-unsaturated ketone

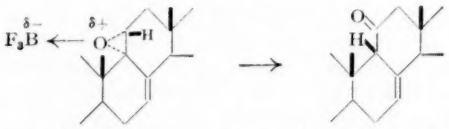
* Part LXI, preceding paper.

was obtained in excellent yield after 18 hours, no appreciable amount of further isomerisation to (VI; R = H, R′ = $C_9H_{17}$) taking place even in 14 days.

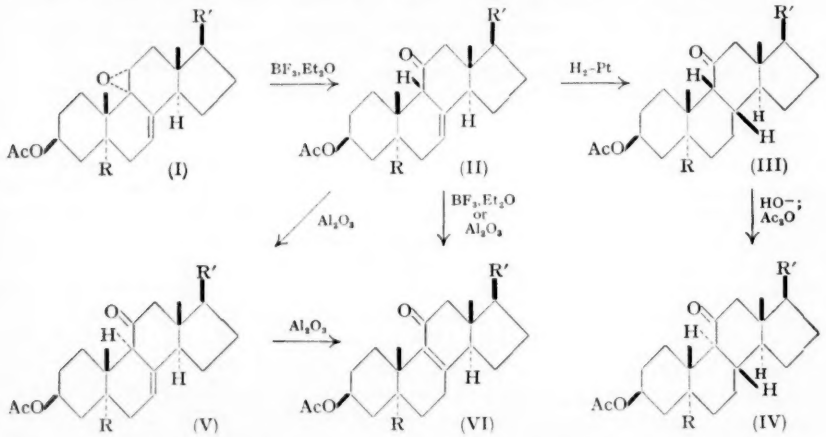
The formulation of the new compound as a $\beta\gamma$-unsaturated ketone followed from its ultra-violet and infra-red light absorption characteristics and from its ready isomerisation to the conjugated ketone (VI; R = H, R′ = $C_9H_{17}$) when treated with boron trifluoride–ether complex in benzene, or with hot acetic acid, or when passed in benzene through activated alumina; each of these three methods gave nearly quantitatively (VI; R = H, R′ = $C_9H_{17}$) of considerably better quality than that obtained by the direct method of the Swiss workers. Further chemical transformations of (II; R = H, R′ = $C_9H_{17}$) clearly indicated the presence at $C_{(9)}$ of a centre of unnatural configuration, a result readily explained by consideration of the mechanism of the rearrangement.

The first step in the isomerisation of the 9α : 11α-epoxide to the 11-keto-$\Delta^7$-9β-steroid must be co-ordination of boron trifluoride with the epoxide group. On the assumption that partial dissociation of the boron trifluoride complex takes place, the reaction can be depicted as :

$$BF_3,Et_2O \rightleftharpoons Et_2O + BF_3$$



Co-ordination takes place rapidly in benzene, whereas in ether the slowness of the rearrangement results from repression of dissociation of the boron trifluoride–ether complex. The isomerisation can then be envisaged as a movement of the $C_{(9)}$-oxygen linkage electrons on to the now electron-deficient oxygen atom with simultaneous movement of the 11β-hydrogen along the β-face of the molecule to the unnatural β-position at $C_{(9)}$.




Evidence for the β-configuration of the hydrogen atom at $C_{(9)}$ in (II; R = H, R′ = $C_9H_{17}$) was provided by the observation that this ketone and its hydrogenation product (see below) could be epimerised to the corresponding 9α-compounds under alkaline conditions. The epimerisation of the 11-keto-$\Delta^7$-9β-compound was complicated to some extent by the ease with which further isomerisation to the conjugated ketone occurred, but a good yield of 3β-acetoxyergosta-7 : 22-dien-11-one (V; R = H, R′ = $C_9H_{17}$) was obtained by passing a benzene solution of (II; R = H, R′ = $C_9H_{17}$) through a column of suitably acid-treated alumina. Inversion at $C_{(9)}$ is accompanied by a comparatively large positive increase in molecular rotation and this appears to be general for all the 11-keto-$\Delta^7$-compounds studied. In view of the ease of inversion at $C_{(9)}$, the normal isomer

may feature as an intermediate in the rearrangement of (II; R = H, R′ = $C_9H_{17}$) to (VI; R = H, R′ = $C_9H_{17}$) and some evidence in support of this is presented in the next paper. An analogy for the fact that the kinetically controlled epimerisation of the $C_{(9)}$-β-hydrogen atom in (II; R = H, R′ = $C_9H_{17}$) takes precedence over the further isomerisation to the more stable conjugated ketone may be found in the experiments of Ingold, de Salas, and Wilson (*J.*, 1936, 1328), who showed that the rate of hydrogen exchange of the activated methylene group in *cyclo*hex-1-enylacetonitrile was much greater than the rate of isomerisation to the conjugated nitrile. This epimerisation at $C_{(9)}$ may be an example of a "concerted displacement reaction" of the type discussed by Swain and his co-workers (*J. Amer. Chem. Soc.*, 1952, **74**, 2534, 2538, and earlier papers); these authors consider that the rate-determining step in the mutarotation of certain sugars is the simultaneous addition and loss of a proton.

The difference in chemical properties between the two isomeric βγ-unsaturated ketones was particularly apparent in their behaviour on hydrogenation. The unnatural configuration at $C_{(9)}$ was first suspected when the ketone (II; R = H, R′ = $C_9H_{17}$) readily absorbed two mols. of hydrogen (one reducing the 22 : 23-bond) in the presence of platinum under neutral or acidic conditions, to afford a new saturated 11-ketostanol (III; R = H, R′ = $C_9H_{19}$). The unprecedented ease of hydrogenation of the 7 : 8-bond clearly indicated that some unusual stereochemical factor must be involved, and confirmation of the suspected abnormal β-configuration at $C_{(9)}$ in the hydrogenation product followed from its epimerisation to the 9α-isomer, although the conditions needed proved to be much more severe than those used in the conversion of (II; R = H, R′ = $C_9H_{17}$) into (V; R = H, R′ = $C_9H_{17}$). Thus the epimerisation of (III; R = H, R′ = $C_9H_{19}$) necessitated heating in strong alcoholic alkali for several hours; the isomeric ketone of natural configuration was then obtained in good yield, its structure being proved by comparison of its 3β-acetate (IV; R = H, R′ = $C_9H_{19}$) with an authentic sample prepared by hydrogenation of 3β-acetoxyergost-22-en-11-one (IV; R = H, R′ = $C_9H_{17}$) (Heusser *et al.*, *loc. cit.*). The conversion of (III; R = H, R′ = $C_9H_{19}$) into (IV; R = H, R′ = $C_9H_{19}$) clearly proves that the enolisable $C_{(9)}$-hydrogen atom in (III), and thus in (II), has the β-orientation. It also shows that the $C_{(8)}$-hydrogen atom introduced by hydrogenation of the 7 : 8-bond in (II) is normally (β-)orientated, and that this reduction must take place by frontal approach of the platinum catalyst rather than by attack on the α-face of the molecule as appears to be the general rule for hydrogenation in the B-, C-, and D-rings in sterols of natural configuration (Fieser, *Experientia*, 1950, **6**, 313).

Hydrogenation of (V; R = H, R′ = $C_9H_{17}$) took a course entirely different from that of the 9β-epimer. Platinum-catalysed reduction in neutral solution resulted in saturation of the side-chain bond, to give 3β-acetoxyergost-7-en-11-one (V; R = H, R′ = $C_9H_{19}$) whose structure was indicated by the absence from the infra-red absorption spectrum of a band associated with the side-chain double bond and also by its conversion into 3β-acetoxyergost-8(9)-en-11-one (VI; R = H, R′ = $C_9H_{19}$) on alumina. Hydrogenation in acidic medium, however, resulted in the formation of the $\Delta^{8(14)}$-compound, α-ergostenyl acetate, the reaction probably proceeding *via* the conjugated ketone, for (VI; R = H, R′ = $C_9H_{17}$), on hydrogenation, also yielded α-ergostenyl acetate, presumably by hydrogenolysis of the 11-keto-group and subsequent migration of the double bond.

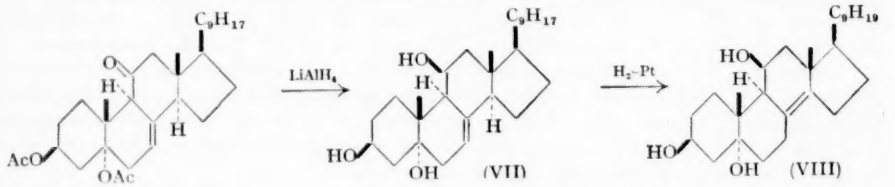
The difference in the course of hydrogenation of (II) and (V) must be related to the unusual conformation of the 9β-epimer. Ring C has approximately a *cyclo*hexanone boat conformation, and the effect of this is to move the angular 18- and 19-methyl groups further apart, thus enhancing the opportunity for frontal attack by the hydrogenation catalyst. Further evidence of the stereospecificity of the hydrogenation of $\Delta^7$-9β-sterols is provided by Müller's observation (*Z. physiol. Chem.*, 1935, **233**, 224) that *iso*pyrocalciferol [identical in configuration at $C_{(9)}$ and $C_{(10)}$ with (II)] takes up 3 mols. of hydrogen, in contrast to the 2 mols. absorbed by pyrocalciferol [different from *iso*pyrocalciferol and (II) in configuration at $C_{(10)}$] or by ergosterol.

11-Keto-steroids of natural configuration containing 5α-hydroxy- or 5α-acetoxy-substituents have been prepared similarly. The monoepoxides (I; R = OH or OAc, R′ = $C_9H_{17}$) have been prepared by selective oxidation of the corresponding 7 : 9-dienes

with monoperphthalic acid, and the chemistry of these compounds provides unequivocal proof that the epoxy-group is located at 9 : 11. The epoxides (I; R = OH or OAc, R′ = $C_9H_{17}$) were isomerised to the corresponding 11-keto-$\Delta^7$-9β-stenols (II) by the boron trifluoride–ether complex, although the rate of rearrangement was appreciably less than with the 5-hydrogen compounds—this indicates steric interference by the more bulky substituents at $C_{(5)}$. Rearrangement of (I; R = OAc, R′ = $C_9H_{17}$) has also been effected by use of the stannic chloride–ether complex in ether–benzene as an example of an alternative Lewis acid; the product being then chromatographed, the 9α-isomer (V; R = OAc, R′ = $C_9H_{17}$) was consequently obtained.

The reduction and isomerisation reactions could be carried out with these 5-hydroxy- and 5-acetoxy-compounds, although again the rates of the various reactions were considerably diminished. The strongly alkaline conditions required for epimerisation of (III; R = OAc, R′ = $C_9H_{19}$) to the corresponding 11-ketone of natural configuration resulted in hydrolysis of the 5α- as well as of the 3β-acetoxy-group, mild acetylation then giving the same product (IV; R = OH, R′ = $C_9H_{19}$) as was obtained in the 5-hydroxy-series. In no instance in this sequence of reactions was there any indication that the hydroxyl substituents at $C_{(5)}$ had been eliminated.

Isomerisation of the unconjugated ketone (II; R = OAc, R′ = $C_9H_{17}$) to the conjugated compound was readily effected by treatment with dilute alkali at room temperature; the monoacetate so obtained was evidently 5α-acetoxy-3β-hydroxyergosta-8(9) : 22-dien-11-one (VI; R = OAc, R′ = $C_9H_{17}$, 3-OH in place of 3-OAc), since it readily afforded a diacetate (VI; R = OAc, R′ = $C_9H_{17}$). Some difficulty, however, was encountered in obtaining the conjugated 5-hydroxy-ketone, treatment of the unconjugated isomer (II; R = OH, R′ = $C_9H_{17}$) with alkali or with acetic acid (or better zinc and acetic acid) leading to incomplete isomerisation (judged spectroscopically). However, the conjugated compound could be isolated by chromatography of such mixtures.

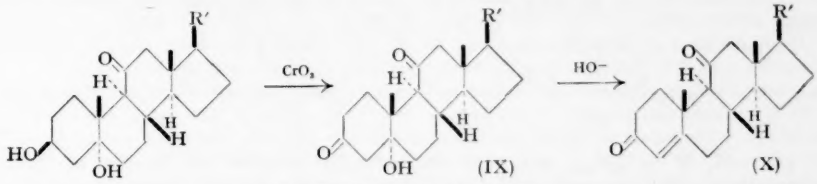



On reduction with lithium aluminium hydride, 3β : 5α-diacetoxyergosta-7 : 22-dien-11-one (V; R = OAc, R′ = $C_9H_{17}$), obtained by epimerisation of the 9β-isomer on alumina, gave an ergostadienetriol (VII); it must contain an 11β-hydroxyl group as only a monoacetate was formed on mild acetylation. Hydrogenation of (VII) with platinum in acetic acid resulted in saturation of the side-chain double bond and also in migration of the nuclear double bond from the 7(8)- to the 8(14)-position, to give ergost-8(14)-ene-3β : 5α : 11β-triol (VIII). Evidence for the location of the double bond in (VIII) is provided by its greater intensity of absorption in the 2050—2250-Å region compared with (VII) (Bladon, Henbest, and Wood, *J.*, 1952, 2737). Platinum-catalysed reduction of (V; R = OAc, R′ = $C_9H_{17}$) in acetic acid (at normal pressure or at 100 atmospheres) resulted only in saturation of the side-chain double bond. The product, 3β : 5α-diacetoxyergost-7-en-11-one (V; R = OAc, R′ = $C_9H_{19}$), was identical with that obtained from the epoxide (I; R = OAc, R′ = $C_9H_{19}$) by rearrangement with the boron trifluoride–ether complex and subsequent epimerisation.

The sequence of reactions (I)—(IV) opens up alternative routes to cortisone and also to its 9-*iso*-analogue. One such approach could involve the selective hydrogenation of the 7 : 8-bond in (II; R = H, R′ = $C_9H_{17}$), leaving the side-chain double bond intact for subsequent degradation. Catalytic hydrogenation with nickel, platinum, or palladium catalysts in neutral or acidic media indicated some preferential reduction of the side-chain rather than the nuclear double bond. However, by starting from ergosteryl-D acetate 22 : 23-dibromide or -dichloride (Anderson, Stevenson, and Spring, *J.*, 1952, 2901), a

similar series of reactions has been used to prepare (III; R = H, R′ = $C_9H_{17}$) (cf. following paper).

Alternatively, by using the procedures described above, the 20-ketone (I; R = OH, R′ = COMe) (cf. previous paper) has been converted into the 11 : 20-diketone (IV; R = OH, R′ = COMe). The strongly alkaline conditions necessary for epimerising the 9β-hydrogen atom in the intermediate compound (III; R = OH, R′ = COMe) are vigorous enough to cause equilibration at $C_{(17)}$ (cf. references given by Elks and Shoppee, *J.*, 1953, 241). However, as with compounds not containing an 11-keto-group, the compound with the side-chain in the natural configuration was the more stable and a good yield of (IV; R = OH, R′ = COMe) could be obtained. The intention in introducing and retaining the 5-hydroxyl group throughout this work has been to facilitate the eventual production of a 3-keto-$\Delta^4$-grouping, and the usefulness of this approach was demonstrated by oxidation of (IV; R = OH, R′ = COMe) to the 3-keto-5-hydroxy-compound (IX; R′ = COMe), which, with dilute alkali, yielded 11-ketoprogesterone (X; R′ = COMe).




(R′ = COMe or CHMe·$CO_2$Me)

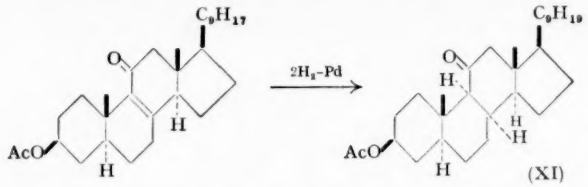
The production of a similar series of compounds containing a –CHMe·$CO_2$H side-chain started from 3β-acetoxy-5α : 8α-epidioxybisnor*allo*chol-9-enic acid, originally obtained as a by-product from the ozonolysis of 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene (Bladon, Henbest, Jones, Wood, and Woods, *J.*, 1952, 4890). The yield of acid can be greatly improved (at the expense of the aldehyde) by decomposing the ozonide with permanganate in acetic acid. Zinc–acetic acid treatment of the acid yielded the corresponding 7 : 9-diene, which could be transformed by the new methods into methyl 3 : 11-diketobisnorchol-4-enate (X; R′ = CHMe·$CO_2$Me).

It is now accepted that the *cyclo*hexane ring is more stable in the chair than in the boat form and therefore that, of a number of possible conformations to represent a given steroid, the one having the most chair forms is to be preferred (Barton, *Experientia*, 1950, **6**, 316; *J.*, 1951, 1048; *J.*, 1953, 1027; Johnson, *Experientia*, 1951, **7**, 315). Comparison of models of the 9α- (IV) and 9β-steroids (III) shows that, whereas the 9α-compound will exist with rings A, B, and C in chair forms, the epimer must have either ring B or ring C in a boat form * (the conformation of the 9β-compounds will be discussed in more detail in a later paper); accordingly, conversion into the compound of natural configuration might be expected when epimerisation of the hydrogen at $C_{(9)}$ is possible (as in III). This example is superficially analogous to the well-known conversion of *cis*-α-decalones into *trans*-α-decalones, but the *trans*-ring fusion is not always more stable, as is exemplified by the failure to isomerise *cis-syn-trans*-perhydro-9-ketophenanthrene to the *trans-syn-trans*-compound (Linstead and Whetstone, *J.*, 1950, 1428). It is significant that the latter compound, unlike the *cis*-isomer, cannot exist with the central ring in a chair form and so has a chair-boat-chair conformation (Johnson, *loc. cit.*). Of interest in relation to these ideas is the palladium-catalysed hydrogenation of 3β-propionoxy-5α : 22*a*-spirost-8(9)-en-11-one to give a saturated steroid, formulated, presumably by virtue of its stability to alkali, as 3β-propionoxy-5α : 8α : 9β : 22*a*-spirostan-11-one (Sondheimer, Yashin, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2696). However, this stability to alkali may not imply the existence of a *trans*-B–C ring fusion since inspection of models of steroids with

* A consequence is that the 18- and 19-methyl groups are further apart in the 9β-compounds (III) than in the 9α-isomers (IV), but the 11-keto-group in (III) is, nevertheless, still too hindered to allow the formation of an oxime or 2 : 4-dinitrophenylhydrazone.

8α-hydrogen atoms shows that the compound with a *cis*-B–C ring-fusion (8α : 9α; Fig. 1) * contains one less *cyclo*hexane boat conformation than the isomer with the unnatural *trans*-B–C ring-fusion (8α : 9β; Fig. 2) (it will be noted that these conformations both contain one more boat ring than the corresponding perhydrophenanthrene compounds discussed above—this is due to the increased rigidity imposed by the *trans*-fused ring D). On this basis the alkali-stable reduction product would, perhaps, best be formulated as 3β-propionoxy-5α : 8α : 22*a*-spirostan-11-one.

In view of the vigorously alkaline conditions required for epimerisation of (III), it was thought desirable to confirm the stability of the type of hydrogenation product prepared by Sondheimer *et al.* Palladium-catalysed hydrogenation of 3β-acetoxyergosta-8(9) : 22-dien-11-one (VI; R = H, R′ = $C_9H_{17}$), under conditions essentially those used by them, afforded a saturated 11-ketostanol, which differed in physical properties from (III) and




(XI)

(IV) (R = H, R′ = $C_9H_{19}$) and must therefore have either the 8α : 9α- or the 8α : 9β-configuration. The change in molecular rotation ($\Delta M_D$ −590°) accompanying saturation of the 8 : 9-bond of the intermediate (VI; R = H, R′ = $C_9H_{19}$) was similar to that of the sapogenin example ($\Delta M_D$ −525°), indicating that the configurations of the two hydro-

FIG. 1.

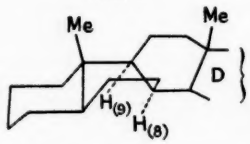
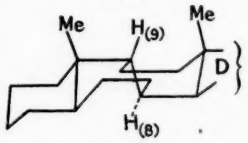



FIG. 2.




genation products about the 8 : 9-bridgehead are probably the same. The stability of the 11-ketostanol to alkali under conditions causing epimerisation at $C_{(9)}$ in (III) was then confirmed. This is best explained if the hydrogenation product is 3β-acetoxy-8α-ergostan-11-one (XI), saturation of the 8 : 9-bond having taken place by normal *cis*-addition of hydrogen.

On the other hand, hydrogenation of the similarly substituted 7-keto-$\Delta^{8(9)}$-system gives saturated ketones of natural configuration (8β : 9α) (cf. Stavely and Bollenback, *ibid.*, 1943, **65**, 1290). It is possible that *cis*-addition to give an 8α : 9α-compound first takes place and that this is succeeded by a ready epimerisation of the 8-hydrogen atom under the conditions of hydrogenation; alternatively, different steric factors may favour 1 : 4-addition of hydrogen to the unsaturated ketone system.

*Addendum.*—Since this paper was prepared for publication, Heusler and Wettstein (*Helv. Chim. Acta*, 1953, **36**, 398) have described the preparation of 3β-acetoxy-9β-ergost-7-en-11-one, m. p. 146—148°, $[\alpha]_D$ −144°, from the corresponding 9α : 11α-epoxide. They describe also the further isomerisation to the conjugated ketone.

## EXPERIMENTAL

For general instructions see preceding paper. A Perkin–Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra.

* Fig. 1 represents the most probable conformation for an 8α : 9α-compound, accounting for the ready conversion of 5α : 8α-dihydroxy-steroids into 5α : 8α-epoxides (Clayton, Henbest, and Jones, *J.*, 1953, 2015). On the assumption that ring A is in a chair form, Fig. 2 represents the only strainless conformation for an 8α : 9β-steroid.

The boron trifluoride–ether complex was freshly distilled before use, and the solvents used in conjunction with this reagent were thoroughly dried over sodium.

*The 5α-hydrogen series.*

3β-*Acetoxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = H, R′ = $C_9H_{17}$).*—(*a*) A solution of pure 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (Heusser *et al.*, *Helv. Chim. Acta*, 1951, **34**, 2106) (5 g.; dried for 3 hr. *in vacuo*) in dry benzene (120 c.c.) was treated with boron trifluoride–ether complex (400 mg.). After 1 min. sodium hydrogen carbonate solution was added, the mixture shaken, and the benzene separated and evaporated under reduced pressure. Crystallisation from acetone afforded the 11-*ketone* (3·9 g.) as blades, m. p. 159—161°, $[\alpha]_D$ −191° (*c*, 1·16) (Found: C, 79·15; H, 10·05. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Light absorption: Max. 2950 Å; ε = 120. Infra-red spectrum (in $CS_2$): peaks at 1736 and 1240 (acetate), 1725 (11-ketone), 1660 ($\Delta^7$), 970 ($\Delta^{22}$), 820 and 810 cm.$^{-1}$ ($C_{(7)}$–H bending).

(*b*) Boron trifluoride–ether complex (6·5 c.c.; 1·15 mols.) was added to a solution of the epoxide (20 g.) in dry ether (2 l.), the solution then being kept at 20° for 20 hr. Crystallisation of the product from chloroform–methanol gave the 11-ketone (17 g.), m. p. 158—160°, $[\alpha]_D$ −182°.

3β-*Acetoxyergosta*-7 : 22-*dien*-11-*one* (V; R = H, R′ = $C_9H_{17}$).—A solution of the foregoing ketone (2 g.) in light petroleum–benzene (2 : 1; 45 c.c.) was adsorbed on alumina (60 g.) (see below). Elution with the same solvent mixture (200 c.c.) and benzene (100 c.c.) gave a solid (1·75 g.) which, on crystallisation from methanol, afforded the 11-*ketone* as hexagonal plates, m. p. 175—180°, $[\alpha]_D$ +25° (Found: C, 79·2; H, 10·15. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Infra-red spectrum (in $CS_2$): peaks at 1735 and 1240 (acetate), 1710 (11-ketone), 1665 ($\Delta^7$), 970 ($\Delta^{22}$), 830 and 800 cm.$^{-1}$ ($C_{(7)}$–H bending).

The alumina used above was prepared as follows: Peter Spence (Grade 0) alumina was treated with 10% aqueous acetic acid, then thoroughly washed with methanol, and reactivated (Brockmann grade II/III) at 100°/12 mm. It is important that the steroid is adsorbed on the column in a solvent of lower polarity than that required to elute the product. With other types of deactivated alumina, it is sometimes necessary to leave the column for several hours (or overnight) before eluting the 9α-isomer.

3β-*Acetoxyergosta*-8(9) : 22-*dien*-11-*one* (VI; R = H, R′ = $C_9H_{17}$).—(*a*) 3β-Acetoxy-9β-ergosta-7 : 22-dien-11-one (320 mg.; dried *in vacuo*) was dissolved in dry benzene (8 c.c.) and treated with boron trifluoride–ether complex (100 mg.; 1 mol.). The specific rotation of the solution changed from −186° to a constant value of +80° after 48 hr. at 20°. Isolation with ether and crystallisation from methanol yielded the conjugated ketone (250 mg.) as blunt needles, m. p. 136—136·5°, $[\alpha]_D$ +105° (*c*, 1·39) (Found: C, 79·3; H, 10·3. Calc. for $C_{30}H_{46}O_3$: C, 79·25; H, 10·2%). Light absorption: Max. 2540 Å; ε = 9200 (Heusser *et al.*, *loc. cit.*, record m. p. 122—123°, $[\alpha]_D$ +92°; $\lambda_{max.}$ 2530 Å, ε = 9500; Schoenewaldt *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 2696, give m. p. 131·5—134°, $[\alpha]_D$ +110°; $\lambda_{max.}$ 2540 Å, ε = 9140). Infra-red spectrum (in Nujol): peaks at 1732 and 1250 (acetate), 1655 and 1640 (11-ketone), 1590 ($\Delta^{8(9)}$), and 970 cm$^{-1}$. ($\Delta^{22}$).

(*b*) The 9β-unconjugated ketone (250 mg.) in acetic acid (8 c.c.) was heated under reflux for 2 hr. Isolation with ether, and recrystallisation from methanol, gave the conjugated ketone (195 mg.) as laths, m. p. 132—134°, $[\alpha]_D$ +95°.

(*c*) A solution of the 9β-unconjugated ketone (250 mg.) in benzene (5 c.c.) was adsorbed on alumina (25 g.). After 45 min. the column was eluted with ether (200 c.c.). Evaporation of the solvent gave a solid which afforded the conjugated ketone (180 mg.), m. p. 135—136°, $[\alpha]_D$ +105°, on crystallisation from methanol.

3β-*Acetoxy*-9β-*ergostan*-11-*one* (III; R = H, R′ = $C_9H_{19}$).—A solution of 3β-acetoxy-9β-ergosta-7 : 22-dien-11-one (250 mg.) in acetic acid (25 c.c.) was shaken with hydrogen and Adams catalyst (25 mg.). Hydrogenation ceased after the uptake of 2 mols. Isolation with ether, followed by crystallisation from methanol, afforded the saturated 11-*ketone* (200 mg.), m. p. 155—156°, $[\alpha]_D$ +43° (*c*, 1·39) (Found: C, 78·75; H, 10·75. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Light absorption: Max. 2920 Å; ε = 31. Infra-red spectrum (in $CS_2$): peaks at 1735 and 1245 (acetate), and 1720 cm.$^{-1}$ (11-ketone). On admixture with 3β-acetoxy-ergostan-11-one (see below) the m. p. was depressed to 113—145°. No derivative was formed with 2 : 4-dinitrophenylhydrazine.

Hydrogenation in dioxan, with Adams catalyst, yielded the same product.

3β-*Acetoxyergostan*-11-*one* (IV; R = H, R′ = $C_9H_{19}$).—A solution of the 9β-compound

* See addendum, p. 2926.

(1 g.) and potassium hydroxide (7·5 g.) in ethanol (50 c.c.) was heated under reflux for 18 hr. The product was isolated with ether and then reacetylated, to give (after crystallisation from aqueous methanol) 3β-acetoxyergostan-11-one (0·78 g.) as needles, m. p. 135—136°, $[\alpha]_D$ +33° (Found: C, 78·5; H, 10·95. Calc. for $C_{30}H_{50}O_3$: C, 78·55; H, 11·0%). The m. p. was not depressed on admixture with an authentic sample obtained by hydrogenation of 3β-acetoxyergost-22-en-11-one in acetic acid with Adams catalyst. Heusser *et al.*, *loc. cit.*, record m. p. 135—136°, $[\alpha]_D$ +32°.

*Hydrogenation of* 3β-*Acetoxyergosta*-7 : 22-*dien*-11-*one*.—(a) *In acetic acid.* The ketone (250 mg.), dissolved in acetic acid (25 c.c.), was shaken in hydrogen with prereduced Adams catalyst (100 mg.); three mols. were taken up in 2 hr. Filtration, evaporation under reduced pressure, and crystallisation from methanol, afforded 3β-acetoxyergost-8(14)-ene (α-ergostenyl acetate) (160 mg.) as plates, m. p. (and mixed m. p. with an authentic sample) 110—112°, $[\alpha]_D$ +1° (*c*, 2·2).

(b) *In dioxan.* Dioxan (25 c.c.) was substituted for acetic acid in experiment (a). Hydrogenation ceased after 5 hr., when 1 mol. of hydrogen had been absorbed. The product was crystallised from methanol, giving crude 3β-acetoxyergost-7-en-11-one, m. p. 145—156°, $[\alpha]_D$ +32°. Further crystallisation did not appreciably change these properties; the infra-red spectrum indicated the presence of acetate and 11-ketone groups and the virtual absence of the $\Delta^{22}$-bond, and analytical data on the mixture were in agreement with $C_{30}H_{48}O_3$. A solution of this material (300 mg.) in benzene (5 c.c.) was adsorbed on alumina (P. Spence, Grade 0, 30 g.). After 15 hr. the column was eluted with benzene (150 c.c.) to give a gum; elution with ether (150 c.c.) gave solid (180 mg.) which crystallised from methanol, to yield 3β-*acetoxyergost*-8(9)-*en*-11-*one* as laths, m. p. 138—140°, $[\alpha]_D$ +119° (*c*, 0·8) (Found: C, 78·95; H, 10·5. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Light absorption: Max. 2540 Å; ε = 9010. Infra-red spectrum in Nujol: peaks at 1732 and 1247 (acetate), 1643 (11-ketone), and 1590 cm.$^{-1}$ ($\Delta^{8(9)}$).* On admixture with a sample of 3β-acetoxyergosta-8(9) : 22-dien-11-one, the m. p. was depressed to 123—133°.

*Hydrogenation of* 3β-*Acetoxyergosta*-8(9) : 22-*dien*-11-*one*.—(a) *In acetic acid.* The ketone (250 mg.) in acetic acid (25 c.c.) was shaken with prereduced Adams catalyst (100 mg.) in hydrogen. Three mols. were taken up in 4 hr. The product, crystallised from methanol, gave 3β-acetoxyergost-8(14)-ene (190 mg.) as plates, m. p. and mixed m. p. 110—112°, $[\alpha]_D$ 0°. The infra-red spectrum was identical with that of an authentic sample.

(b) *In ethanol.* The ketone (2·5 g.) in ethanol (150 c.c.) was shaken with 4% palladised charcoal (2·05 g.) under hydrogen for 18 hr. The gummy product was chromatographed on alumina (P. Spence, Grade 0, 60 g.). Elution with light petroleum–benzene (1 : 1) gave material (1·1 g.) which on crystallisation from methanol afforded 3β-*acetoxy*-8α-*ergostan*-11-*one* (XI) (705 mg.) as plates, m. p. 162—164°, $[\alpha]_D$ −11° (Found: C, 78·75; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Infra-red spectrum (in $CS_2$): peaks at 1732 and 1240 (acetate) and 1698 cm.$^{-1}$ (11-ketone).

Attempted isomerisation of the above compound (500 mg.), by heating it with a solution of potassium hydroxide (4 g.) in ethanol (25 c.c.) for 18 hr., yielded unchanged material (after reacetylation).

*The 5α-hydroxyl series.*

3β-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene*-5α-*ol* (I; R = OH, R′ = $C_9H_{17}$).—An ethereal solution of monoperphthalic acid (1·4 mols.) was added to 3β-acetoxyergosta-7 : 9 : 22-trien-5α-ol (Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood, and Woods, *J.*, 1952, 4883) (1·75 g.) dissolved in dry ether (200 c.c.), and the mixture was kept at 0° for 24 hr. and then at 25° for 48 hr. The steroid was isolated with ether and then absorbed on deactivated alumina (200 g.) from benzene–light petroleum (1 : 1). Elution with the same solvent mixture (4·8 l.) gave crude diepoxide. Elution with benzene (5·2 l.) gave the 9α : 11α-*epoxide*, which crystallised from *iso*propyl ether as plates (570 mg.), m. p. 229—237°, $[\alpha]_D$ +2° (*c*, 1·06) (Found: C, 76·65; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). The compound showed no significant absorption above 2200 Å. Infra-red spectrum (in $CS_2$): peaks at 3500 (hydroxyl), 1735 (acetate), and 968 cm.$^{-1}$ ($\Delta^{22}$).

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = OH, R′ = $C_9H_{17}$).—The above epoxide (5·6 g.) in dry benzene (175 c.c.) was treated with boron trifluoride–ether complex

* The preparation of this compound by a different method has recently been described by Laubach, Schreiber, Agnello, Lightfoot, and Brunings (*J. Amer. Chem. Soc.*, 1953, **75**, 1514), who report m. p. 137·8—138·6° and $\alpha]_D$ +125° (in $CHCl_3$).

(0·46 g.). The solution became slightly yellow during 5 min.; then aqueous sodium hydrogen carbonate was added with shaking. The steroid was crystallised from acetone to give the *hydroxy-ketone* (first crop, 4·35 g.; m. p. 173—182°, $[\alpha]_D$ −129°; second crop, 0·55 g., $[\alpha]_D$ −124°). Recrystallisation gave the pure product as blades, m. p. 181—187°, $[\alpha]_D$ −135° (*c*, 0·9) (Found: C, 76·3; H, 9·9. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2930 Å; $\varepsilon = 190$. Infra-red spectrum (in Nujol): peaks at 3530 (hydroxyl), 1725 (acetate), 1700 (11-ketone), and 1660 cm.$^{-1}$. ($\Delta^7$).

3β-*Acetoxy*-5α-*hydroxyergosta*-8(9) : 22-*dien*-11-*one* (VI; R = OH, R′ = $C_9H_{17}$).—The foregoing ketone (1 g.) in acetic acid (50 c.c.) was heated to boiling with zinc dust (3 g.). After 5 min., more zinc dust (7 g.) was added and the mixture heated under reflux for 3½ hr. The product (0·95 g.), isolated with ether, had $[\alpha]_D$ +53°; $\lambda_{max.}$ 2550 Å; $\varepsilon = 6300$. Crystallisation of this material raised the rotation slightly but did not raise the ε value at 2550 Å. The total product was chromatographed on deactivated alumina (100 g.), and material of $[\alpha]_D$ +20° to +60° was eluted with light petroleum–benzene (1 : 1), followed by a solid (0·43 g.) with $[\alpha]_D$ +80° eluted with benzene. Crystallisation of the latter product from methanol and then from acetone yielded the conjugated *ketone* as needles, m. p. 192—197°, $[\alpha]_D$ +81° (*c*, 0·89) (Found: C, 76·4; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2570 Å; $\varepsilon = 9200$. The yield estimated by spectroscopic examination of the total reaction product was not altered by different reaction times (from 1 to 18 hr.), $\varepsilon_{max.}$ always being *ca.* 6500.

If the zinc was omitted from the experiment, the reaction proceeded more slowly and somewhat less completely, a constant ε value of 5100 being reached after about 5 hr.

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergostan*-11-*one* (III; R = OH, R′ = $C_9H_{19}$).—3β-Acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (250 mg.) in acetic acid (10 c.c.) was shaken in hydrogen with Adams catalyst (50 mg.); 2 mols. were taken up during 45 min. The product, dissolved in acetone (15 c.c.), was treated with 0·5 c.c. of 8N-chromic acid in dilute sulphuric acid for 10 min.; isolation with ether and crystallisation from methanol gave the *ketone*, m. p. 171—173°, $[\alpha]_D$ +88° (*c*, 0·95) (Found: C, 75·95; H, 10·55. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Light absorption: Max. 2880 Å; $\varepsilon = 45$. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1730 (acetate), and 1690 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α-*hydroxyergostan*-11-*one* (IV; R = OH, R′ = $C_9H_{19}$).—A solution of the foregoing ketone (100 mg.) and potassium hydroxide (1 g.) in 95% methanol (10 c.c.) was heated under reflux for 18 hr. Isolation with ether, followed by crystallisation from acetone, gave the 3 : 5-diol (75 mg.) as needles, m. p. 228—231° (decomp.), $[\alpha]_D$ +39·5°. This diol, with acetic anhydride and pyridine at 20° overnight, afforded the 3-*acetoxy*-11-*ketone* (plates from methanol), m. p. 208—212°, $[\alpha]_D$ +24·5° (*c*, 1·02) (Found: C, 75·85; H, 10·75. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Infra-red spectrum (in Nujol): peaks at 3490 (hydroxyl), 1735 (acetate), and 1693 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α : 8α-*epidioxybisnor*allo*chol*-9-*enic Acid*.—3β-Acetoxy-5α : 8α-epidioxyergosta-9(11) : 22-diene (Bladon *et al.*, *J.*, 1952, 4883) (20 g.) in ethyl acetate (1·5 l.) was treated with ozone at −70° until a blue colour persisted. After being allowed to warm to room temperature the solution was treated with potassium permanganate (10 g.) in water (170 c.c.) and acetic acid (200 c.c.). Air was passed through the mixture for 50 min. Excess of permanganate and manganese dioxide were removed by treatment with sodium hydrogen sulphite, the organic layer then being washed with water and then with 0·5N-sodium carbonate. Acidification of the alkaline washings precipitated 3β-acetoxy-5α : 8α-epidioxybisnor*allo*chol-9-enic acid (7·7 g.), m. p. 199—201°. For this compound Bladon *et al.* (*J.*, 1952, 4890) record m. p. 201—205°.

3β-*Acetoxy*-5α-*hydroxybisnor*allo*chola*-7 : 9(11)-*dienic Acid*.—The above acid (10 g.) was treated with zinc dust (20 g.) in refluxing acetic acid (200 c.c.). The steroid was isolated with chloroform; crystallisation from acetone yielded the *diene acid* (7·2 g.) as needles, m. p. 225—227°, $[\alpha]_D$ +54° (*c*, 1·1) (Found: C, 71·7; H, 8·4. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). Light absorption: Max. 2425 Å; $\varepsilon = 15{,}500$. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1732 and 1250 (acetate), 1700 and 1275 cm.$^{-1}$ (carboxyl).

Treatment of the acid with diazomethane gave the methyl ester, which crystallised from methanol as needles, m. p. 193—195°, $[\alpha]_D$ +71° (*c*, 0·9) (Found: C, 72·3; H, 8·6. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%). (Bladon *et al.*, *J.*, 1952, 4890, give m. p. 191—193° $[\alpha]_D$ +69°). Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1732 and 1250 cm.$^{-1}$ (acetate). Light absorption: Max. 2425 Å; $\varepsilon = 16{,}700$.

*Methyl* 3β-*Acetoxy*-9α : 11α-*epoxy*-5α-*hydroxybisnor*allo*chol*-7-*enate* (I; R = OH, R′ = CHMe·$CO_2$Me).—A solution of monoperphthalic acid in ether (99 c.c., containing 4·28 mg. of active oxygen per c.c.; 1·1 mols.) was added to methyl 3β-acetoxy-5α-hydroxybisnor*allo*chola-

7 : 9-dienate (10 g.) in dioxan (200 c.c.). After 24 hr. at 0°, and 48 hr. at 20° the solution was diluted with ethyl acetate and washed successively with water, sodium hydrogen carbonate solution, and water. After removal of the solvent *in vacuo*, crystallisation of the residue from acetone gave the *epoxide* (5·1 g.) as prisms, m. p. 204—206°, $[\alpha]_D$ +15° (*c*, 1·03) (Found: C, 69·4; H, 8·2. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Infra-red spectrum (in Nujol): peaks at 3300 (hydroxyl), 1730 and 1250 cm.$^{-1}$ (acetate).

*Methyl* 3β-*Acetoxy*-5α-*hydroxy*-11-*keto*-9β-*bisnor*allo*chol*-7-*enate* (II; R = OH, R′ = CHMe·$CO_2$Me).—The 9α : 11α-epoxide (500 mg.) in dry benzene (50 c.c.) was treated with boron trifluoride–ether complex (5 drops) and set aside for 5 min. Isolation with ether and crystallisation from methanol yielded needles of the 11-*ketone* (300 mg.), m. p. 171—172°, $[\alpha]_D$ −109° (*c*, 1·97) (Found: C, 69·55; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Infra-red spectrum (in $CS_2$): peaks at 3520 (hydroxyl), 1735 and 1242 (acetate), 1708 (11-ketone), 1166 (ester), 830 and 810 cm.$^{-1}$ ($C_{(7)}$–H bending).

*Methyl* 3β-*Acetoxy*-5α-*hydroxy*-11-*keto*-9β-*bisnor*allo*cholanate* (III; R = OH, R′ = CHMe·$CO_2$Me).—A solution of the foregoing $\Delta^7$-compound (200 mg.) in acetic acid (2 c.c.) was shaken in hydrogen with Adams catalyst (20 mg.), 1 mol. being taken up during 12 min. Filtration, evaporation under reduced pressure, and crystallisation of the residue from methanol gave the saturated *ketone* (120 mg.) as plates, m. p. 187°, $[\alpha]_D$ +84° (Found: C, 69·45; H, 8·85. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%). Infra-red spectrum (in $CS_2$): peaks at 3420 (hydroxyl), 1734 and 1238 (acetate), 1734 and 1158 (ester) and 1703 cm.$^{-1}$ (11-ketone).

*Methyl* 3β-*Acetoxy*-5α-*hydroxy*-11-*ketobisnor*allo*cholanate* (IV; R = OH, R′ = CHMe·$CO_2$Me).—The corresponding 9β-compound (500 mg.) and potassium hydroxide (3·5 g.) in ethanol (25 c.c.) were heated under reflux for 15 hr. Acidification and extraction with ether gave the organic acid which was treated with diazomethane in ethereal solution, and then with acetic anhydride in pyridine, to yield the *ketone* (135 mg.), m. p. 215—218° (from methanol), $[\alpha]_D$ +18·5° (*c*, 0·65) (Found: C, 69·45; H, 8·9. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%). Infra-red spectrum (in $CS_2$): peaks at 3600 (hydroxyl), 1732 and 1236 (acetate), 1735 and 1156 (ester), 1702 cm.$^{-1}$ (11-ketone). If the acetylation stage was omitted, the corresponding 3 : 5-*diol* was obtained as needles, m. p. 187—191°, $[\alpha]_D$ +46° (*c*, 0·92) (Found: C, 70·5; H, 9·25. $C_{23}H_{36}O_5$ requires C, 70·35; H, 9·25%). Infra-red spectrum (in Nujol): peaks at 3600 and 3450 (hydroxyl), 1741 and 1160 (ester), and 1690 cm.$^{-1}$ (11-ketone).

*Methyl* 5α-*Hydroxy*-3 : 11-*diketobisnor*allo*cholanate* (IX; R′ = CHMe·$CO_2$Me).—Chromium trioxide in dilute sulphuric acid (0·5 c.c.; 7·5N, with respect to active oxygen) was slowly added to a solution of the above diol (400 mg.) in acetone (5 c.c.) at 40°. Isolation with ether, followed by crystallisation from aqueous acetone, gave the *diketone* (260 mg.) as plates, m. p. 222—226°, $[\alpha]_D$ +58° (Found: C, 70·9; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3460 (hydroxyl), 1735 and 1170 (ester), 1710 and 1716 cm.$^{-1}$ (11- and 20-ketones).

The 2 : 4-dinitrophenylhydrazone formed rapidly with Brady's reagent as a yellow solid, quickly changing to a red solid shown to be the 2 : 4-*dinitrophenylhydrazone* of methyl 3 : 11-diketobisnorchol-4-enate. From a warm solution only the red solid was precipitated. The derivative crystallised from methanol–chloroform as needles, m. p. 248—250° (Found: C, 63·1; H, 6·4; N, 10·45. $C_{29}H_{36}O_7N_4$ requires C, 63·0; H, 6·6; N, 10·1%). Light absorption: Max. 2250 (ε = 18,500) and 3820 Å (ε = 33,000).

*Methyl* 3 : 11-*Diketobisnorchol*-4-*enate* (X; R′ = CHMe·$CO_2$Me).—The above diketone (95 mg.) in ethanol (30 c.c.) was treated with potassium hydroxide solution (33%; 0·45 c.c.) and then kept at 20° for 70 min. Isolation with ether gave solid (80 mg.) which, on crystallisation from aqueous methanol, afforded *methyl* 3 : 11-*diketobisnorchol*-4-*enate* as needles, m. p. 170°, $[\alpha]_D$ +86° (*c*, 0·6) (Found: C, 74·2; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%). Light absorption: Max. 2370 Å; ε = 10,000. Infra-red spectrum (in Nujol): peaks at 1742 and 1160 (ester), 1711 (11-ketone), 1678 (3-ketone), and 1620 cm.$^{-1}$ ($\Delta^4$).

3β-*Acetoxy*-5α-*hydroxy*allo-9β-*pregn*-7-*ene*-11 : 20-*dione* (II; R = OH, R′ = COMe).—A solution of the corresponding 9α : 11α-epoxide (cf. preceding paper) (190 mg.; dried *in vacuo* at 80°) in dry benzene (10 c.c.) was treated with boron trifluoride–ether complex at 20°. After 5 min., the pale yellow solution was shaken with aqueous potassium hydrogen carbonate, dried, and evaporated. Crystallisation from methanol–*iso*propyl ether gave plates (140 mg.), m. p. 175—182°; the pure *ketone* had m. p. 182—183°, $[\alpha]_D$ −61° (*c*, 0·67) (Found: C, 71·1; H, 8·35. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). Infra-red spectrum (in Nujol): peaks at 3480 (hydroxyl), 1717 (acetate and 20-ketone), 1705 (11-ketone), 1657 ($\Delta^7$), and 1250 cm.$^{-1}$ (acetate).

3β-*Acetoxy*-5α-*hydroxy*allo-9β-*pregnane*-11 : 20-*dione* (III; R = OH, R′ = COMe).—The fore-

going $\Delta^7$-compound (120 mg.) in acetic acid (12 c.c.) was shaken with hydrogen and prereduced Adams's catalyst (50 mg.). Between 2 and 3 mols. of hydrogen were taken up, and the mixture of dihydroxy(and possibly trihydroxy)-compounds was oxidised by treating the crude hydrogenation product in acetone (10 c.c.) at 40° with chromic acid solution [0·2 c.c. of a solution of chromic acid (6·7 g.) in sulphuric acid (5·35 c.c.) and water (20 c.c.)]. After 3 min., water was added and the steroid extracted with ether. The *diketone* (80 mg.) crystallised from methanol–*iso*propyl ether as needles, m. p. 177—179°, $[\alpha]_D$ +180° (*c*, 1·21) (Found: C, 71·0; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3390 (hydroxyl), 1730 (acetate and 20-ketone), 1690 (11-ketone), and 1250 cm.$^{-1}$ (acetate). In one experiment (3 mol. uptake), the product was crystallised from methanol–*iso*propyl ether, affording 3β-*acetoxy*-9β-allo*pregnane*-5α : 11ξ : 20ξ-*triol*, m. p. 240—250°, $[\alpha]_D$ +39° (*c*, 1·0) (Found: C, 70·1; H, 9·8. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%). The infra-red spectrum confirmed the presence of hydroxyl and acetate groups.

3β-*Acetoxy*-5α-*hydroxy*allo*pregnane*-11 : 20-*dione* (IV; R = OH, R′ = COMe).—The 9β-isomer (135 mg.) and potassium hydroxide (1 g.) in methanol (5 c.c.) and water (0·5 c.c.) were heated under reflux for 6 hr. Isolation with ether, followed by mild acetylation, gave a product which on crystallisation from chloroform–*iso*propyl ether afforded material (100 mg.), m. p. 240—250°. The pure *diketone* had m. p. 257—261°, $[\alpha]_D$ +79·5° (*c*, 0·66) (Found: C, 70·85; H, 8·85. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3485 (hydroxyl), 1720 (acetate and 20-ketone), 1690 (11-ketone), and 1245 cm.$^{-1}$ (acetate). Rehydrolysis of the material in the mother-liquor and reacetylation gave more material, probably owing to equilibration at $C_{(17)}$.

11-*Ketoprogesterone* (X; R′ = COMe).—3β-Acetoxy-5α-hydroxy*allo*pregnane-11 : 20-dione (70 mg.) was hydrolysed by hot 2% methanolic potassium hydroxide for 1 hr. The diol, obtained by ether-extraction of the acidified solution, was dissolved in acetone (7·5 c.c.) at 40° and treated with 0·15 c.c. of a solution of chromic acid (6·7 g.) in sulphuric acid (5·35 c.c.) and water (20 c.c.). After 2 min., the product was isolated with ether; crystallisation from methanol–*iso*propyl ether gave the 5-hydroxy-3-ketone (27 mg.) as prisms, m. p. 250°, $[\alpha]_D$ +123° (*c*, 0·41). This was dissolved in ethanol (10 c.c.) containing potassium hydroxide (0·2 g.) and kept at 20° for 1½ hr. Acidification and isolation with ether gave material that was absorbed on alumina (2 g.); the residue from the benzene eluates gave, after 3 crystallisations from methanol–*iso*propyl ether, 11-ketoprogesterone as needles, m. p. 170—173° (not depressed on admixture with a sample kindly supplied by Dr. C. Djerassi), $[\alpha]_D$ +234° (*c*, 0·63). Infra-red spectrum (in Nujol): peaks at 1700 (11- and 20-ketones), 1665 (3-ketone), 1615 ($\Delta^4$), and 871 cm.$^{-1}$ ($C_{(4)}$–H bending); the spectrum was identical with that of Dr. Djerassi's sample.

*The 5α-acetoxyl series.*

3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene* (I; R = OAc, R′ = $C_9H_{17}$).—3β : 5α-Diacetoxyergosta-7 : 9(11) : 22-triene (Bladon *et al.*, *J.*, 1952, 4883) (7·63 g.) in ether (150 c.c.) was treated at 0° with monoperphthalic acid in ether (31·0 c.c.; 1·105N; 1·1 mols.), the solution then being kept at 0° for 24 hr. and at 20° for 48 hr. The solution was washed successively with water, sodium hydrogen carbonate solution, water, ferrous sulphate solution, and water, and then evaporated to dryness. Crystallisation of the residue from aqueous acetone gave the *epoxide* as needles (6·9 g.), m. p. 125—127°, $[\alpha]_D$ +57·5° (*c*, 0·7) (Found: C, 74·75; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). The compound showed no significant absorption above 2200 Å. Infra-red spectrum (in $CS_2$): peaks at 1740—1730 and 1240 (acetates), 968 ($\Delta^{22}$), and 807 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = OAc, R′ = $C_9H_{17}$).—The above epoxide (10 g.) and boron trifluoride–ether complex (5 c.c.) in dry benzene (150 c.c.) and dry ether (350 c.c.) were kept at 20° for 3 hr. Treatment with sodium hydrogen carbonate solution, followed by evaporation of the organic solvent, yielded an oil which was dissolved in acetone (50 c.c.). Water (5 c.c.) was added and the solution was cooled to 0°, whereupon the *mono-acetone solvate* of the 11-ketone (8·5 g.) separated as rosettes of needles, melting at 77°, resolidifying by 115°, and melting again at 140—143°, $[\alpha]_D$ −45° (Found: C, 73·3; H, 9·3. $C_{32}H_{48}O_5,C_3H_6O$ requires C, 73·65; H, 9·55%). The acetone was easily removed by warming the solvate *in vacuo* and the product then crystallised from methanol, affording the 11-*ketone* as rods, m. p. 140—143°, $[\alpha]_D$ −49° (Found: C, 74·75; H, 9·5. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Infra-red spectrum (in $CS_2$): peaks at 1730 (acetate and 11-ketone), 1664 ($\Delta^7$), 1244 (acetate), 968 ($\Delta^{22}$), and 805 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxy*-9β-*ergostan*-11-*one* (III; R = OAc, R′ = $C_9H_{19}$).—The foregoing ketone

(4 g., of acetone solvate) in acetic acid (50 c.c.) was shaken in hydrogen with Adams catalyst (400 mg.); two mols. were absorbed in 10 min. The product, the 11-*ketone*, crystallised from methanol as plates (3 g.), m. p. 127—130°, $[\alpha]_D$ +64° (Found: C, 74·25; H, 10·0. $C_{32}H_{52}O_5$ requires C, 74·35; H, 10·15%). Infra-red spectrum (in $CS_2$): peaks at 1740, 1728 and 1240—1230 (acetates), and 1728 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α-*hydroxyergostan*-11-*one* (IV; R = OH, R′ = $C_9H_{19}$).—A solution of the foregoing ketone (2 g.) and potassium hydroxide (10 g.) in ethanol (100 c.c.) was heated under reflux for 20 hr. Isolation with chloroform and crystallisation from ethanol gave a good yield of 3β : 5α-*dihydroxyergostan*-11-*one* as rods, m. p. 229—235°, $[\alpha]_D$ +37° (Found: C, 77·5; H, 10·9. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Infra-red spectrum (in Nujol): peaks at 3500 and 3200 (hydroxyl), and 1700 cm.$^{-1}$ (11-ketone). Acetylation with acetic anhydride and pyridine at 20° gave the 3-acetate (IV; R = OH, R′ = $C_9H_{19}$) identical in a mixed m. p. determination and infra-red spectrum with a specimen prepared by the route described above.

3β : 5α-*Diacetoxyergosta*-7 : 22-*dien*-11-*one* (V; R = OAc, R′ = $C_9H_{17}$).—The isomeric 9β-compound (200 mg.) was adsorbed from light petroleum–benzene (1 : 1) solution on to alumina [acid washed, see preparation of (V; R = H, R′ = $C_9H_{17}$)] (30 g.). The column was eluted with benzene to yield, after 2 crystallisations from ethanol, the 11-*ketone* (85 mg.) as needles, m. p. 174—178°, $[\alpha]_D$ +84° (Found: C, 74·65; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Infra-red spectrum (in $CS_2$): peaks at 1735 and 1240 (acetate), 1710 (11-ketone), 1667 ($\Delta^7$), 968 ($\Delta^{22}$), and 805 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (VI; R = OAc, R′ = $C_9H_{17}$) (with D. C. Eaton).—3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (9α- or 9β-epimer) (1 g.), dissolved in methanol (50 c.c.), was treated with 2% methanolic sodium hydroxide (50 c.c.) The solution was kept at 20° for 1 hr., and the steroid then isolated with ether and reacetylated with acetic anhydride and pyridine at 20° overnight. The isomeric *diacetate* (0·8 g.) crystallised from methanol as laths, m. p. 150—153°, $[\alpha]_D$ +121° (*c*, 1·3) (Found: C, 74·85; H, 9·65. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Light absorption: Max. 2540 Å; ε = 9000. Infra-red spectrum (in $CCl_4$): peaks at 1735 (acetate), and 1665 cm.$^{-1}$ (11-ketone).

If the reacetylation was omitted, 5α-*acetoxy*-3β-*hydroxyergosta*-8 : 22-*dien*-11-*one* could be obtained by crystallisation from methanol. It formed needles, m. p. 128—131°, $[\alpha]_D$ +103° (*c*, 0·67) (Found: C, 76·5; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2540 Å; ε = 8800.

3β : 5α-*Diacetoxyergost*-7-*en*-11-*one* (V; R = OAc, R′ = $C_9H_{19}$).—(*a*) 3β : 5α-Diacetoxy-9α : 11α-epoxyergost-7-ene (cf. preceding paper) (500 mg.) in dry benzene (15 c.c.) was treated with 1 drop of boron trifluoride–ether complex. The measured rotation of the solution changed from +2·16° to +0·03° (constant) during 2 days. Isolation with ether, and chromatography of the product on deactivated alumina (50 g.), afforded the ketone (220 mg.) (eluted with 1 : 1 light petroleum–benzene). Recrystallisation from aqueous methanol gave the pure *ketone* as small needles, m. p. 143—147°, $[\alpha]_D$ +104° (*c*, 0·75) (Found: C, 75·0; H, 9·95. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%).

(*b*) 3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (500 mg.) in acetic acid (100 c.c.) was shaken with Adams catalyst (100 mg.) for 1 hr. under hydrogen at 100 atm. The product, isolated in the usual way, crystallised from methanol as needles, m. p. 153—157°, $[\alpha]_D$ +104° (*c*, 1·2) (Found: C, 74·5; H, 10·1. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%). Infra-red spectrum (in Nujol): peaks at 1740 and 1250 (acetate), and 1710 cm.$^{-1}$ (11-ketone).

*Ergosta*-7 : 22-*diene*-3β : 5α : 11β-*triol* (VII).—3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (0·8 g.) in ether (20 c.c.) was slowly added to a solution of lithium aluminium hydride (0·4 g.) in ether under nitrogen. The mixture was refluxed for 3 hr., then poured on ice, and the resulting aluminium hydroxide precipitate was dissolved in a small excess of aqueous tartaric acid. Isolation with chloroform, and crystallisation from acetone, gave the *triol* (0·6 g.) as plates, m. p. 235—236°, $[\alpha]_D$ −25° (*c*, 1·9) (Found: C, 77·5; H, 10·8. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%). Light absorption: Max. 2060 Å; ε = 6070. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 968 ($\Delta^{22}$), 829 and 809 cm.$^{-1}$ ($C_{(7)}$–H bending). The compound gave a yellow colour with tetranitromethane.

Acetylation gave the 3-*monoacetate*, which crystallised from alcohol as prisms, m. p. 217—218°, $[\alpha]_D$ −8° (*c*, 1·0) (Found: C, 76·3; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·25; H, 10·25%). Infra-red spectrum (in Nujol): peaks at 3600—3400 (hydroxyl), 1730 and 1275 (acetate), 966 ($\Delta^{22}$), 834 and 806 cm.$^{-1}$ ($C_{(7)}$–H bending).

*Ergost*-8(14)-*ene*-3β : 5α : 11β-*triol* (VIII).—The preceding triol (300 mg.) in acetic acid (50 c.c.) was shaken with hydrogen in the presence of Adams catalyst (300 mg.) for 5 hr.

Removal of the catalyst, and evaporation of the solvent, gave a solid which was crystallised twice from acetone; *ergost*-8(14)-*ene*-3β : 5α : 11β-*triol* was obtained as plates, m. p. 193—196°, $[\alpha]_D$ +18° (*c*, 1·0) (Found : C, 78·0; H, 11·3. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Light absorption : Apparent max. 2070—2080 Å; ε = 10,000.

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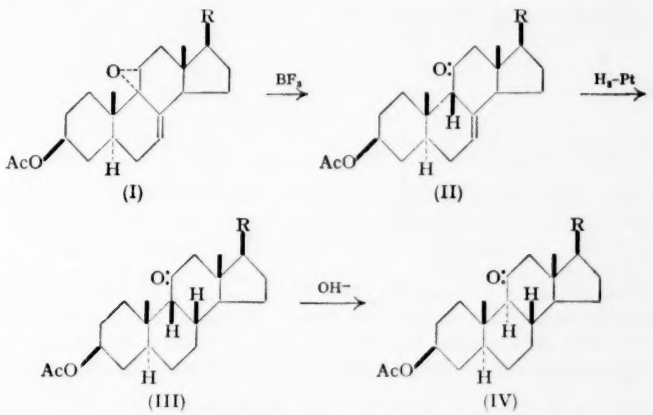
## 585. *Studies in the Synthesis of Cortisone. Part II.* A New Synthesis of 3β-Acetoxyergost-22-en-11-one.*

By J. ELKS, R. M. EVANS, C. H. ROBINSON, G. H. THOMAS, and L. J. WYMAN.

Ergosteryl-D acetate 22 : 23-dibromide or dichloride has been converted into 3β-acetoxyergost-22-en-11-one by the route to 11-keto-steroids described in the previous paper.

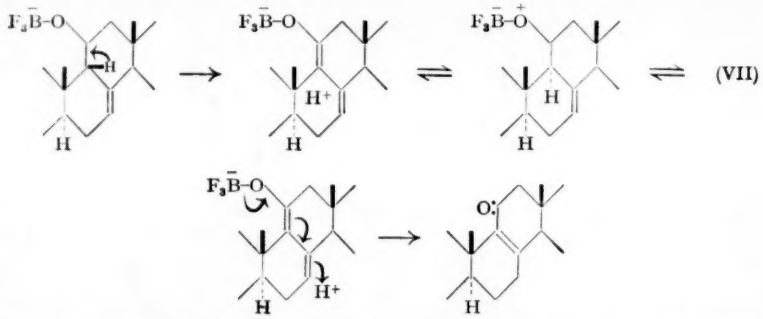
IN Part I * of this series a new method has been described for introducing an 11-keto-group into *allo*steroids. This may be illustrated as follows :



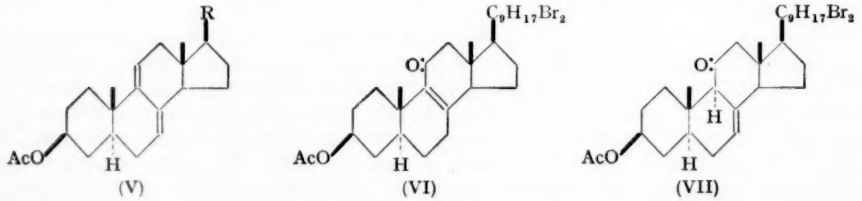

The present paper describes the extension of this route to include the preparation of 3β-acetoxyergost-22-en-11-one (IV; R = $C_9H_{17}$), a key intermediate in the synthesis of cortisone from ergosterol (cf. Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Chemerda, Chamberlin, Wilson, and Tishler, *ibid.*, p. 4053; Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28; Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615). Owing to the rather similar reduction rates of the 7 : 8- and 22 : 23-double bonds in (II; R = $C_9H_{17}$), this compound could not be converted directly into 3β-acetoxy-9β-ergost-22-en-11-one (III; R = $C_9H_{17}$) by selective hydrogenation (see Part I). However, the possibility of protecting the side-chain double bond during this stage as its dibromo-derivative was suggested by the observations of Budziarek, Johnson, and Spring (*J.*, 1953, 534) that such bromine atoms are stable under hydrogenation conditions but are easily removed, with restoration of the 22 : 23-double bond, by the use of zinc.

* Part I, preceding paper.

Since 3β-acetoxy-22 : 23-dibromo-9β-ergost-7-en-11-one (II; R = $C_9H_{17}Br_2$) could not be obtained by direct addition to the $\Delta^{22}$-compound, owing to the ease with which nuclear bromination occurred even at −50°, attention was turned to the rearrangement of 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergost-7-ene (I; R = $C_9H_{17}Br_2$). Preparation of this epoxide from the diene (V; R = $C_9H_{17}Br_2$) and its conversion into 3β-acetoxy-22 : 23-dibromoergost-8(9)-en-11-one (VI), by means of boron trifluoride in benzene, have already been described (Budziarek, Johnson, and Spring, *J.*, 1952, 3410). Parallel with the observations recorded in Part I, we found that by using either a different solvent or a much shorter reaction time this rearrangement could be stopped at the required intermediate βγ-unsaturated ketone (II; R = $C_9H_{17}Br_2$). Thus, in acetone, ethyl acetate, or ether rearrangement was slow (owing to co-ordination of the solvent with boron trifluoride), and the βγ-unsaturated ketone separated from solution in good yield. However, this method was limited in scale by the poor solubility of the epoxide in such solvents. In benzene or toluene, rearrangement was very rapid; since the solution remained homogeneous, it was necessary to stop the reaction at the optimum time by addition of pyridine. With 5% solutions of the epoxide at room temperature, the optimum reaction time was only *ca.* 15 sec., but in toluene at −35° an 80% yield was obtained after 15 min. Reaction beyond the optimum time resulted in lower yields through the formation, first, of the 9α-isomer (VII) and then of the 11-keto-$\Delta^{8(9)}$-compound (VI). It thus appears that the rearrangement of 3β-acetoxy-22 : 23-dibromo-9β-ergost-7-en-11-one to the conjugated unsaturated ketone (VI) involves, as its first stage, inversion of configuration at $C_{(9)}$ (cf. chart).




Hydrogenation of (II; R = $C_9H_{17}Br_2$) to (III; R = $C_9H_{17}Br_2$) presented difficulties not met in the examples described in the previous paper. The poor solubility of the βγ-unsaturated ketone in acetic acid necessitated the addition of chloroform or dioxan, and platinum-catalysed hydrogenation in such solvent mixtures was found to be appreciably slower than




(V) (VI) (VII)

that of, for instance, (II; R = $C_9H_{17}$) in acetic acid alone. Further, a considerable proportion of the material was isomerised to the 11-keto-$\Delta^{8(9)}$-compound. Debromination of (III; R = $C_9H_{17}Br_2$) with zinc readily yielded 3β-acetoxy-9β-ergost-22-en-11-one (III; R = $C_9H_{17}$), and evidence that this still retained the 9β-configuration was provided by reduction to 3β-acetoxy-9β-ergostan-11-one (III; R = $C_9H_{19}$), identical with the compound obtained by hydrogenation of (II; R = $C_9H_{17}$) (cf. Part I).

Returning now to the hydrogenation of (II; R = $C_9H_{17}Br_2$), further investigation

showed that no advantage could be gained by working at higher temperatures (70—100°) in neutral or acidic media, or by adding sodium acetate or catalytic amounts of hydrochloric acid, since these modifications tended to favour isomerisation irrespective of the catalyst used (*viz.*, platinum, palladium–carbon, or Raney nickel). However, a substantial improvement in yield was obtained by hydrogenation at elevated pressure, perhaps because the rate of hydrogenation is more influenced by the concentration of hydrogen on the catalyst surface than is the rate of isomerisation. The reduction product obtained by this method was best purified after debromination; α-dihydroergosteryl acetate was obtained as a by-product (see Experimental section). Thus, platinum-catalysed hydrogenation of (II; R = $C_9H_{17}Br_2$) at 100 atmospheres pressure in chloroform–acetic acid with subsequent debromination gave 3β-acetoxy-9β-ergost-22-en-11-one in 70—74% yield.

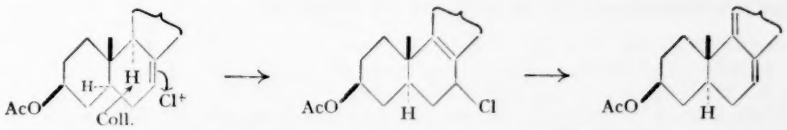
Clearly there was less isomerisation if hydrogenation was rapid. If, then, the slowness of hydrogenation at atmospheric pressure was in some measure caused by poisoning of the catalyst by traces of hydrogen bromide (derived by hydrogenation of the side-chain halogens), it might be advantageous to use the corresponding dichloro-compound (II; R = $C_9H_{17}Cl_2$). 3β-Acetoxy-22 : 23-dichloro-9α : 11α-epoxyergost-7-ene (I; R = $C_9H_{17}Cl_2$), required in the preparation of (II; R = $C_9H_{17}Cl_2$), was obtained by selective oxidation of 3β-acetoxy-22 : 23-dichloroergosta-7 : 9(11)-diene (V; R = $C_9H_{17}Cl_2$). We have now devised a more direct method for preparing this diene than that described by Anderson, Stevenson, and Spring (*J.*, 1952, 2901). Treatment of α-dihydroergosteryl acetate with chlorine at −20° to +20° gave only a poor (isolated) yield of the desired dichloride, but a marked improvement was obtained on adding collidine (or pyridine) to the mixture before chlorination. Adding the base after the chlorine was ineffective. Some illustrative results are summarised in Table 1,

TABLE 1.

| Reaction conditions | Properties of crude total product $[\alpha]_D$ (*c*, 2·0) | 7 : 9(11)-Diene (%) * |
|---|---|---|
| No addition of collidine | −66° | 49 |
| Collidine (2 mols.) added after chlorine | −57 | 48 |
| Collidine (7 mols.) added | + 5 | 82 |
| Collidine (2·2 mols.) added | + 9 | 84 |
| Collidine (0·75 mol.) added | 0 | 82 |

* Based on ε = 19,000 at 242 mμ for pure diene (see Experimental).

the yields of the crude diene being assessed from light-absorption data; purification was wasteful. Collidine did not prevent subsequent addition of hydrogen chloride to the 7 : 9(11)-diene system. A convenient explanation of its action is that it removes the potential proton at $C_{(9)}$ *at the same time* as the original 7(8)-ethylenic linkage is attacked by $Cl^+$, *viz.*:




Rearrangement of 3β-acetoxy-22 : 23-dichloro-9α : 11α-epoxyergost-7-ene to 3β-acetoxy-22 : 23-dichloro-9β-ergost-7-en-11-one (II; R = $C_9H_{17}Cl_2$) proceeded normally in ether. With a platinum catalyst in acetic acid, the uptake of hydrogen by the latter compound was high (*ca.* 2 mols.), hydrogenolysis of the 11-keto-group occurring to a considerable extent, and of the halogen atoms to some extent. When the reaction was stopped after uptake of 1 mol., there was some indication of incomplete reduction of the 7 : 8-double bond. The required compound, 3β-acetoxy-22 : 23-dichloro-9β-ergostan-11-one (III; R = $C_9H_{17}Cl_2$) was best obtained, although in poor yield, by platinum-catalysed hydrogenation in ethyl acetate. Modifying the conditions of hydrogenation, as for the dibromo-compound, was not a substantial improvement. Dehalogenation of (III; R = $C_9H_{17}Cl_2$) with zinc in acetic acid required more vigorous conditions than that of the bromo-compound; in spite of this, there was no indication of epimerisation, and 3β-acetoxy-9β-ergost-22-en-11-one was obtained, identical with the product described earlier.

Finally, prolonged treatment of the 11-keto-$\Delta^{22}$-9β-stanol (III; R = $C_9H_{17}$) with hot ethanolic potassium hydroxide, with subsequent reacetylation, gave in excellent yield the required 3β-acetoxyergost-22-en-11-one (IV; R = $C_9H_{17}$), identical with authentic material (cf. Heusser, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106). Of the two routes to this compound examined, the first, involving the use of 22 : 23-dibromo-compounds, is by far the better and appears to offer a useful alternative to those already described (cf., *inter alia*, *idem*, *ibid.*; Chamberlin *et al.*, *loc. cit.*; Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696).

TABLE 2.

| Compound | $[M]_D$ 9β- | 9α- | $\Delta[M]_D$ 9β ⟶ 9α |
|---|---|---|---|
| IX; R = H, R′ = $C_9H_{17}$ | + 90° | + 55° | − 35° |
| IX; R = H, R′ = $C_9H_{17}Br_2$ | +185 | +110 † | − 75 |
| IX; R = H, R′ = $C_9H_{17}Cl_2$ | +170 | + 95 † | − 75 |
| IX; R = H, R′ = $C_9H_{19}$ * | +195 | +150 | − 45 |
| IX; R = OH, R′ = $C_9H_{19}$ * | +415 | +115 | −300 |
| IX; R = OH, R′ = CHMe·$CO_2$Me * | +365 | + 80 | −285 |
| IX; R = OH, R′ = $COCH_3$ * | +700 | +310 | −390 |
| VIII; R = H, R′ = $C_9H_{17}$ * | −865 | +115 | +970 |
| VIII; R = H, R′ = $C_9H_{17}Br_2$ | −750 | + 80 | +830 |
| VIII; R = OAc, R′ = $C_9H_{17}$ * | −250 | +430 | +680 |

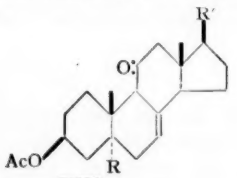
* Part I, *loc. cit.* † Obtained by addition of the necessary halogen to (IV; R = $C_9H_{17}$).

TABLE 3. *Absorption maxima* (*cm.*$^{-1}$), *in* $CS_2$.

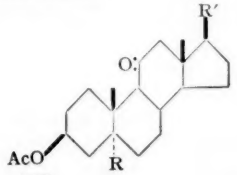
| Compound | 9α-Isomer Acetyl | 9α-Isomer Ketone | 9β-Isomer Acetyl | 9β-Isomer Ketone |
|---|---|---|---|---|
| VIII; R = H, R′ = $C_9H_{17}$ | 1735 | 1710 | 1736 | 1725 |
| VIII; R = H, R′ = $C_9H_{17}Br_2$ | 1736 | 1718 | 1737 | 1726 |
| IX; R = H, R′ = $C_9H_{17}$ (C.S. nos.: 9α-, C.S. 49; 9β-, C.S. 50 *) | 1731 | 1706 | 1734 | 1712 |
| IX; R = H, R′ = $C_9H_{19}$ | 1735 | 1715 | 1735 | 1720 |
| IX; R = H, R′ = $C_9H_{17}Br_2$ | 1732 | 1708 | 1736 | 1715 |
| IX; R = H, R′ = $C_9H_{17}Cl_2$ | 1730 | 1705 | 1737 | 1716 |

* Spectra thus marked have been deposited at the Chemical Society. Photocopies may be obtained from the General Secretary. In such requests the C.S. number must be cited.

Tables 2 and 3 show that regular changes in molecular rotation and infra-red absorption accompany epimerisation at $C_{(9)}$. Thus, inversion at $C_{(9)}$ (β⟶α) in (IX; R = H) leads to a small negative change in molecular rotation (Table 2). The strong vicinal effect of a hydroxy-group at $C_{(5)}$ is apparent from the marked increase in magnitude of the Δ value for compounds (IX; R = OH); a 7 : 8-ethylenic linkage, as in (VIII), increases the Δ value and changes its sign. It is proposed, in a later paper, to show that the molecular-rotation difference is also influenced by the nature of the side-chain.



(VIII)



(IX)

Compared with the corresponding natural isomers, the 9β-compounds (VIII; R = H) and (IX; R = H) show a characteristic displacement of the carbonyl band in the infra-red towards the higher wave-numbers (Table 3), leading to a less well-defined resolution of the acetyl and carbonyl bands.

## EXPERIMENTAL

Unless otherwise specified, optical measurements were determined on chloroform solutions (*c*, 0·9—1·2) at room temperature. Other general experimental directions are given in *J.*, 1953, 2918).

*3β-Acetoxy-22 : 23-dibromo-9β-ergost-7-en-11-one* (II; R = $C_9H_{17}Br_2$).—(*a*) A solution of

3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergost-7-ene (Budziarek, *et al.*, *J.*, 1952, 3410) (50 g.) in toluene (1·5 l.) was concentrated to 1 l. at atmospheric pressure. With exclusion of moisture, the solution was treated with freshly distilled boron trifluoride–ether complex (10 ml.; 1 mol.) for 15 min. at −35°. Pyridine (20 ml.) was then added to the solution, which, after warming to room temperature, was washed successively with water, aqueous sodium hydrogen carbonate, and water, and concentrated *in vacuo* to 200 ml.; on addition of ethanol (1 l.) and cooling in the refrigerator, needles (41 g., 82%) separated with m. p. 195—197°, $[\alpha]_D$ −120°. Crystallisation from benzene afforded the 11-*ketone* as needles, m. p. 196—198°, $[\alpha]_D$ −123° (Found: C, 58·6; H, 7·65. $C_{30}H_{46}O_3Br_2$ requires C, 58·65; H, 7·55%). The compound showed no selective absorption of high intensity above 220 mμ. Infra-red spectrum (in $CS_2$): peaks at 1737 and 1240 (acetate), 1726 (11-ketone), 1656, 821, and 805 cm.$^{-1}$ (trisubstituted nuclear double bond).

The mother-liquors were evaporated to dryness *in vacuo*; crystallisation of the residue from ethyl acetate gave 3β-*acetoxy*-22 : 23-*dibromoergost*-7-*en*-11-*one* (VII) as plates, m. p. 217—219°, $[\alpha]_D$ −13° (Found: C, 58·65; H, 7·7%). This showed no selective absorption of high intensity above 220 mμ. Infra-red spectrum (in $CS_2$): peaks at 1736 and 1238 (acetate) and 1718 cm.$^{-1}$ (11-ketone).

(*b*) Freshly distilled boron trifluoride–ether complex (2 ml.; 1 mol.) was added to a solution of the 9α : 11α-epoxide (10 g.) in dry ether (500 ml.), the solution then being kept at 0° for 18 hr.; the 9β-compound (7·8 g., 78%) separated as needles, m. p. 193—196°, $[\alpha]_D$ −118°.

*Hydrogenation of* 3β-*Acetoxy*-22 : 23-*dibromo*-9β-*ergost*-7-*en*-11-*one*.—(a) *At atmospheric pressure.* A solution of the above βγ-unsaturated ketone (5 g.) in chloroform–acetic acid (1 : 1; 20 ml.) was shaken with Adams catalyst (2 g.) under hydrogen until 1 mol. of hydrogen was absorbed (*ca.* 1 hr.). Isolation with ether followed by crystallisation from ethyl acetate gave 3β-*acetoxy*-22 : 23-*dibromo*-9β-*ergostan*-11-*one* (III; R = $C_9H_{17}Br_2$) (2·17 g., 54%) as laths, m. p. 226—230° (decomp.), $[\alpha]_D$ +30° (Found: C, 58·6; H, 7·95. $C_{30}H_{48}O_3Br_2$ requires C, 58·45; H, 7·85%). Infra-red spectrum (in $CS_2$): peaks at 1736 and 1242 (acetate) and 1715 cm.$^{-1}$ (11-ketone).

The second crop from the above crystallisation had $\lambda_{max.}$ 252 mμ ($E^{1\%}_{1cm}$ 135) in EtOH. Hydrogenation of (II; R = $C_9H_{17}Br_2$) under the above conditions, but on a larger scale (17 g.), gave the saturated dibromo-ketone in 30% yield.

*Debromination.* Zinc dust (10 g.) was added, during 1 hr., to a stirred solution of the foregoing ketone (2 g.) in chloroform (40 ml.) and acetic acid (80 ml.), at <50°. After being stirred for a further hour at room temperature, the solution was filtered and diluted with water. Isolation with chloroform, followed by crystallisation from chloroform–methanol, gave 3β-*acetoxy*-9β-*ergost*-22-*en*-11-*one* (III; R = $C_9H_{17}$) (1·2 g., 81%) as plates, m. p. 170—173°, $[\alpha]_D$ +20° (Found: C, 78·9; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Infra-red spectrum (in $CS_2$): peaks at 1734 and 1240 (acetate), 1712 (11-ketone), and 970 cm.$^{-1}$ ($\Delta^{22}$).

(b) *At elevated pressure.* The 9β-unconjugated ketone (37·5 g.) in chloroform–acetic acid (1 : 1; 670 ml.) was shaken with Adams's catalyst (3·35 g.) under hydrogen at 100 atm. for 30 min. The solution was filtered and treated with zinc dust (50 g.) as described above. Isolation with chloroform, followed by crystallisation from methanol–chloroform, gave 3β-acetoxy-9β-ergost-22-en-11-one (20·7 g., 74%) as plates, m. p. 170—174°, $[\alpha]_D$ +18·5°.

It was not always possible to purify the 11-ketone by crystallisation alone, without undue wastage; in such instances chromatography was used. Crude material (7 g.) [prepared as above from 10 g. of (III; R = $C_9H_{17}Br_2$)] was adsorbed on alumina (P. Spence, Grade 0, 180 g.); the first fractions obtained on elution with light petroleum–benzene (3 : 1; 2 × 100 ml.) had $[\alpha]_D$ <+15°—these were discarded. Material obtained by elution with light petroleum–benzene (3 : 1; 300 ml.) and benzene (300 ml.) was crystallised from chloroform–methanol to give the 11-ketone (5·2 g., 70%) as plates, m. p. 167—169°, $[\alpha]_D$ +20°. Repeated crystallisation from methanol of the combined fractions with $[\alpha]_D$ <+15° (see above) gave α-dihydroergosteryl acetate as plates, m. p. 174—178°, $[\alpha]_D$ −18·5° (Found: C, 82·25; H, 11·05. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%). Barton and Cox (*J.*, 1948, 1354) give m. p. 181°, $[\alpha]_D$ −19°, −20°. On admixture with authentic material the m. p. was not depressed. The corresponding alcohol had m. p. 170—174°, $[\alpha]_D$ −18° (Found: C, 84·3; H, 11·5. Calc. for $C_{28}H_{46}O$: C, 84·35; H, 11·6%) (*idem*, *ibid.*, give m. p. 176°, $[\alpha]_D$ −19°). Admixture with authentic material did not depress the m. p.

3β-*Acetoxy*-9β-*ergostan*-11-*one* (III; R = $C_9H_{19}$).—3β-Acetoxy-9β-ergost-22-en-11-one (100 mg.) was hydrogenated with prereduced Adams catalyst (30 mg.) in acetic acid (100 ml.). One mol. of hydrogen was absorbed. Isolation with ether followed by crystallisation from methanol gave the 11-ketone (45 mg.) as rods, m. p. and mixed m. p. 151—152°, $[\alpha]_D$ +45° (cf. Part I).

3β-*Acetoxyergost*-22-*en*-11-*one* (IV; R = $C_9H_{17}$).—A solution of the 9β-isomer (2 g.) and potassium hydroxide (20 g.) in ethanol (150 ml.) was heated under reflux for 18 hr. The product was isolated with ether and reacetylated with acetic anhydride (24 ml.) and pyridine (20 ml.) at 100° for 1 hr. Crystallisation from methanol gave the 11-ketone (1·69 g., 85%) as needles, m. p. 124—125°, $[\alpha]_D$ +12° (Found: C, 78·8; H, 10·5. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%). Admixture with an authentic sample did not depress the m. p. (cf. Heusser *et al.*, *loc. cit.*, who record m. p. 125—126°, $[\alpha]_D$ +12·5°). The infra-red spectrum was identical with that of authentic material.

Addition of water to the mother-liquors from the above crystallisation gave further 11-ketone (90 mg., 4·6%) with m. p. 119—123°, $[\alpha]_D$ +11·8°.

3β-*Acetoxy*-22 : 23-*dibromoergostan*-11-*one* (IV; R = $C_9H_{17}Br_2$).—Bromine (1·55 g., 1·1 mols.) in chloroform (6 ml.) was added dropwise to 3β-acetoxyergost-22-en-11-one (4 g.) in chloroform (20 ml.); rapid decolorisation ensued. On addition of methanol (100 ml.) and cooling to 0°, needles (1·2 g.) separated with m. p. 225—231°; $[\alpha]_D$ +16·7°. Crystallisation from ethanol gave the 11-*ketone* 22 : 23-*dibromide* as needles, m. p. 233—236°, $[\alpha]_D$ +18·5° (Found: C, 58·2; H, 7·9. $C_{30}H_{48}O_3Br_2$ requires C, 58·4; H, 7·85%). Infra-red spectrum (in $CS_2$): bands at 1732 and 1242 (acetate), and 1708 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-22 : 23-*dichloroergosta*-7 : 9(11)-*diene* (V; R = $C_9H_{17}Cl_2$).—To α-dihydroergosteryl acetate (10 g.) in carbon tetrachloride (150 ml.) and redistilled collidine (6 ml.) at 0°, chlorine (4 g.) in carbon tetrachloride (500 ml.) was added slowly with stirring. The mixture was left at room temperature with stirring, for 1 hr., and then washed successively with 2N-hydrochloric acid and water. Removal of the carbon tetrachloride by distillation on the steam-bath at atmospheric pressure, followed by crystallisation of the residue from chloroform–methanol, gave needles (6·3 g., 55%), m. p. 204—207° (decomp.), $[\alpha]_D$ +33° (*c*, 1·94). Recrystallisation from chloroform–methanol afforded the 7 : 9(11)-diene as needles, m. p. 227—229° (decomp.), $[\alpha]_D$ +45° (*c*, 2) (Found: C, 70·6; H, 9·05; Cl, 14·0. Calc. for $C_{30}H_{46}O_2Cl_2$: C, 70·7; H, 9·1; Cl, 13·9%). Light absorption: Max. at 242 (ε = 19,000) and 235 mμ (ε = 17,000). Anderson *et al.*, *loc. cit.*, record m. p. 235—237°, $[\alpha]_D$ +44°.

The corresponding *alcohol*, prepared from the acetate with potassium hydroxide in methanol–dioxan, crystallised from chloroform–methanol in blades, m. p. 210—212° (decomp.), $[\alpha]_D$ +37·4° (*c*, 1·4) (Found: Cl, 15·2. $C_{28}H_{44}OCl_2$ requires Cl, 15·3%). Light absorption: Max. at 243 (ε = 20,000) and 235 mμ (ε = 18,300).

*Treatment of* 3β-*Acetoxy*-22 : 23-*dichloroergosta*-7 : 9 (11)-*diene with Hydrogen Chloride*.—The diene (330 mg.) in carbon tetrachloride (22 ml.) containing hydrogen chloride (55 mg.), was stirred for 30 min. at 0°. The solvent was evaporated *in vacuo*, leaving a solid, m. p. 225—227° (decomp.) (undepressed on admixture with starting material), $[\alpha]_D$ +41°. Light absorption: Max. at 242 (ε = 18,900) and 235 mμ (ε = 17,000).

3β-*Acetoxy*-22 : 23-*dichloro*-9α : 11α-*epoxyergost*-7-*ene*.—An ethereal solution of monoperphthalic acid (40 ml. containing 1·3 equivs. of available oxygen) was added to a cooled solution of 3β-acetoxy-22 : 23-dichloroergosta-7 : 9(11)-diene (10·5 g.) in chloroform (freshly distilled over anhyd. $K_2CO_3$; 100 ml.) at such a rate that the temperature did not exceed −5°. After being left for 2 hr. at 0°, the mixture was washed successively with aqueous sodium hydrogen carbonate, dilute aqueous ferrous sulphate, and water. The solution was then dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was triturated with hot acetone (30 ml.), cooled, and filtered off. The *epoxide* (7·4 g., 68%) melted at 191—197° and had $[\alpha]_D$ −14°. Crystallisation from ethyl acetate gave the compound as needles, m. p. 204—208°, $[\alpha]_D$ −18·5° (Found: C, 68·5; H, 8·6. $C_{30}H_{46}O_3Cl_2$ requires C, 68·55; H, 8·8%). Infra-red spectrum (in Nujol): bands at 1730 and 1240 (acetate) and 1652 and 833 cm.$^{-1}$ (trisubstituted ethylene).

3β-*Acetoxy*-22 : 23-*dichloro*-9β-*ergost*-7-*en*-11-*one* (II; R = $C_9H_{17}Cl_2$).—Freshly distilled boron trifluoride–ether complex (1·3 ml., 1 mol.) was added to 3β-acetoxy-22 : 23-dichloro-9α : 11α-epoxyergost-7-ene (5·25 g.) in dry ether (500 ml.), the solution then being kept at 0° for 18 hr. The 11-*ketone dichloride* (2·9 g., 55%) separated as needles, m. p. 217—222°, $[\alpha]_D$ −134° (Found: C, 68·4; H, 8·5. $C_{30}H_{46}O_3Cl_2$ requires C, 68·55; H, 8·8%). The compound showed no significant absorption above 220 mμ. Infra-red spectrum (in $CS_2$): bands at 1738 and 1240 (acetate), 1726 (11-ketone), 1657, 820, and 808 cm.$^{-1}$ (associated with trisubstituted nuclear double bond). The ethereal filtrate was washed successively with water, sodium hydrogen carbonate solution, and water, and evaporated until solid began to separate; the crystals were collected and crystallised from ethyl acetate, to give the 11-ketone dichloride (1·08 g., 20·6%), $[\alpha]_D$ −122°.

3β-*Acetoxy*-22 : 23-*dichloro*-9β-*ergostan*-11-*one* (III; R = $C_9H_{17}Cl_2$).—The foregoing ketone (2·63 g.) in ethyl acetate (250 ml.) was hydrogenated in the presence of prereduced Adams catalyst (500 mg.), 2·2 mols. of hydrogen being absorbed in 65 min. Filtration, evaporation of the solvent, and repeated crystallisation of the residue from methanol gave the 11-*ketone dichloride* (650 mg., 25%) as plates, m. p. 248—252°, $[\alpha]_D$ +32° (Found : C, 68·4; H, 9·1; Cl, 13·1. $C_{30}H_{48}O_3Cl_2$ requires C, 68·3; H, 9·1; Cl, 13·45%). Infra-red spectrum (in $CS_2$) : bands at 1737 and 1240 (acetate), and 1716 cm.$^{-1}$ (11-ketone).

*Dechlorination.* Zinc dust (5 g.) was added during 1 hr. to a solution of the above ketone (570 mg.) in refluxing acetic acid (50 ml.), and heating was continued for 4 hr. Isolation with chloroform and crystallisation from methanol gave 3β-acetoxy-9β-ergost-22-en-11-one (340 mg., 74%), identical in a mixed m. p. determination and infra-red spectrum with a specimen prepared by the alternative route described above.

3β-*Acetoxy*-22 : 23-*dichloroergostan*-11-*one* (IV; R = $C_9H_{17}Cl_2$).—Chlorine (2 g., 3 mols.) in carbon tetrachloride (150 ml.) was added dropwise to 3β-acetoxyergost-22-en-11-one (5 g.) in pyridine (250 ml.) and carbon tetrachloride (150 ml.) at 0°. After 1 hr. at room temperature, the solution was washed with 2N-hydrochloric acid and water. Evaporation *in vacuo* followed by crystallisation from methanol–chloroform gave the 11-*ketone dichloride* as needles, m. p. 212—215°, $[\alpha]_D$ +18° (Found : C, 68·2; H, 9·1; Cl, 13·2. $C_{30}H_{48}O_3Cl_2$ requires C, 68·3; H, 9·1; Cl, 13·45%). Infra-red spectrum (in $CS_2$) : bands at 1730 and 1240 (acetate), and 1705 cm.$^{-1}$ (11-ketone).

We acknowledge our indebtedness to Dr. D. H. R. Barton for his interest in and advice on the work described here, to Dr. J. E. Page for determining infra-red spectra, to Miss H. King for carrying out microanalyses, and to Mr. W. F. Wall for experimental assistance. One of us (C. H. R.) wishes also to thank the Nuffield Foundation for a financial grant.

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## 586. *Olefin Co-ordination Compounds. Part III.* Infra-red Spectra and Structure : Attempted Preparation of Acetylene Complexes.*

By J. CHATT and L. A. DUNCANSON.

The infra-red spectra of five olefin complexes with platinous chloride show that the olefin exists, with its double bond, in the complex. The C=C stretching frequency is lowered by some 143 wave-numbers, about twice the lowering observed for silver-ion complexes. These facts and all data relating to olefin complexes of $Pd^{II}$, $Pt^{II}$, $Cu^{I}$, $Ag^{I}$, and $Hg^{II}$ in the literature are consistent with a structure schematically shown in the Figures, essentially Dewar's structure (*Bull. Soc. chim.*, 1951, **18**, C 79), and with no other structure yet proposed.

From the dipole moments of compounds of the type $C_2H_4$.am,$PtCl_2$ (am = amine) we estimate that the $C_2H_4 \longrightarrow Pt$ bond moment is about 2 D less (or greater) than that of the $N \longrightarrow Pt$ bond. If we assume that this difference is due only to double-bond formation as required by the above structure, it indicates not more than about ⅓ double-bond character in the $C_2H_4$–Pt bond. Hel'man's evidence for the quadrivalency of platinum in olefin complexes of platinous chloride is shown to be consistent with bivalency. The chlorination of $(C_2H_4PtCl_2)_2$ yields ultimately ethylene dichloride, but not in the first stages of the chlorination. A much improved preparation of $(C_2H_4PtCl_2)_2$ has been found. Attempts to prepare platinous chloride complexes of but-2-yne and of diphenylacetylene were unsuccessful.

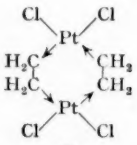
IN Parts I (*J.*, 1949, 3340) and II * the previously proposed structures of olefin complexes were reviewed and all were shown to be unsatisfactory. It was also suggested (Part I) that some sort of bond involving the participation of an electron pair from filled *d*-orbitals of the metal atom, in addition to the ordinary co-ordinate bond, was essential for olefin co-ordination. This bond was envisaged as being similar in nature to the π-bond which,

* Part II, *J.*, 1952, 2622.

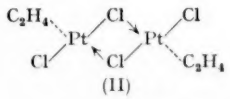
as Pauling (" Nature of the Chemical Bond," Cornell Univ. Press, 1939) proposed, might exist between the carbon and nickel atoms in nickel carbonyl; however, it was difficult to formulate such a bond between a platinum atom and the two carbon atoms of an olefin.

Hel'man (*Compt. rend. Acad. Sci., U.R.S.S.*, **1939**, **24**, 549) had previously proposed an apparently similar mode of binding the olefin to the platinum. Her structure is vaguely described and differs from our preliminary suggestions in two important ways. It allows only one molecule of the olefin to be attached to one platinum atom, but the carbonyl-like structure would allow more than one, and in Part II we described the preparation of $(C_2H_4)_2PtCl_2$. Her structure requires that the platinum atom in $K[C_2H_4PtCl_3]$ be formally quadrivalent, the carbonyl-like structure that it be formally bivalent. She preferred structure (I) for ethylene platinous chloride [" Complex Compounds of Platinum with Unsaturated Molecules," Soviet Acad. Sci., 1945 (in Russian); cf. Kharasch and Ashford, *J. Amer. Chem. Soc.*, **1936**, **58**, 1733]. The present work shows that propylene exists, with its double bond, in propylene platinous chloride. This disposes of such structures as (I) and illustrates the essential difference between her conception of the olefin-to-platinum bond and ours. We consider ethylene platinous chloride to have a halogen-bridged structure (II) as originally suggested by Pfeiffer (" Organische Molekülverbindungen," Verlag von Ferdinand Enke, Stuttgart, 1927, p. 209), the only remaining problem being the nature of the $C_2H_4$–Pt bond.

Olefins belong to the class of ligands which form only weak, if any, complexes with boron trihalides and related substances but combine fairly strongly with platinous chloride. Other such substances are CO, $PF_3$, and to a lesser extent, tertiary alkyl-phosphines, -arsines, and other ligands in which the donor atom has a low electronegativity. They are all substances with a vacant orbital or a potentially vacant orbital in the valency shell of the donor atom; this orbital is available for $\pi$-bond formation by overlap with a filled *d*-orbital of the metal atom. It was on the basis of such considerations that we predicted the carbon monoxide-like behaviour of $PF_3$, and the possible existence of volatile $Ni(PF_3)_4$ (Chatt, *Nature*, **1950**, **165**, 859) which has since been confirmed (Wilkinson, *J. Amer. Chem. Soc.*, **1951**, **73**, 5501; Chatt and Williams, *J.*, **1951**, 3061; see also Chatt and Wilkins, *J.*, 1952, 4300).



(I)



(II)

The above class of ligands, the individual members of which readily form covalent dihalides (*e.g.*, $COCl_2$, $PF_3Cl_2$, $C_2H_4Cl_2$), we consider to be bound in platinous complexes by bonds of partial double-bond character. They are characterised by their tendency to labilise substituents in the *trans*-position to themselves in platinous complexes; thus substitution occurs rapidly in that position. On the other hand, those ligands which cannot accommodate more electrons (*i.e.*, do not form covalent dihalides) direct substituents into the *cis*-positions, and substitution occurs rather slowly.

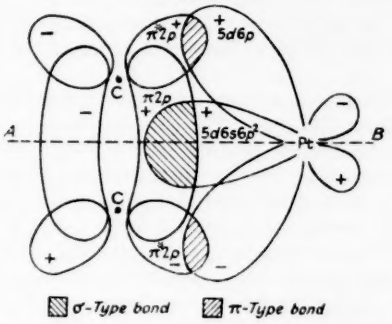
Because olefins are among the most strongly *trans*-directing ligands (Chernyaev and Hel'man, *Compt. rend. Acad. Sci., U.R.S.S.*, N.S., **1936**, **4**, 181) we consider that they are bound to the metal by a $\sigma$- and a $\pi$-type of bond. To satisfy these requirements we proposed the ethylidene structure for $[C_2H_4PtCl_3]^-$ (Chatt, *Research*, **1951**, **4**, 180). A second structure also satisfying these requirements, but without the objectionable feature of the migration of a hydrogen atom, was proposed at about the same time by Dewar (*Bull. Soc. chim.*, **1951**, **18**, C 79). It was proposed with particular reference to the silver-ion complexes, but in its adaptation to the platinous complexes the $\sigma$-type bond would be formed by overlap of a $5d6s6p^2$ hybrid orbital of the platinum atom with the $\pi$-orbital of the olefin, and the $\pi$-type bond by overlap of a filled 5*d*-orbital of the metal atom with the antibonding $\pi$-molecular orbital of the olefin. The $\pi$-type bond would be

strengthened, however, by hybridisation of the 5*d*-orbital with the vacant 6*p*-orbital of the platinum atom to give a *dp*-hybrid more suitably shaped than the unhybridised 5*d*-orbital to provide a large overlap with the antibonding orbitals of the olefin (Craig, Maccoll, Nyholm, Orgel, and Sutton, personal communication). This gives us the picture of the olefin–platinum bond which is shown schematically in the Figures.

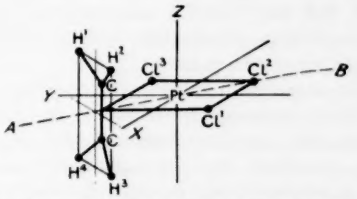
The new data which we present here show that the ethylidene structure is untenable, but accord with the above structure. A review of the properties of olefin–metal salt complexes, showing how they can all be correlated on the basis of Dewar's structure, was given at a conference in March, 1952 (Chatt, " The General Chemistry of Olefin Complexes with Metallic Salts " in " Cationic Polymerisation and Related Complexes," Ed. P. H. Plesch, Heffer, Cambridge, 1953). We shall, therefore, consider only the new data in this communication.

*Infra-red Spectra.*—The infra-red spectra of powdered crystalline complexes of olefins with platinous chloride have shown that the olefin retains its double bond in the complex and is symmetrically co-ordinated to the platinum. It is well established that olefinic C–H stretching modes of vibration cause absorption at frequencies greater than 3000 cm.$^{-1}$ (Fox and Martin, *Proc. Roy. Soc.*, 1938, *A*, **167**, 257; 1940, *A*, **175**, 208; Pozefsky and

*Orbitals used in the combination of ethylene with platinum.*




*Spatial arrangement of atoms in* $[C_2H_4PtCl_3]^-$.




(The plane of the hydrogen atoms is parallel to the plane $Cl^1ZCl^3$ but probably displaced slightly from co-planarity with the carbon atoms by the repulsion of the hydrogen atoms by the platinum atom.)

Coggershall, *Analyt. Chem.*, 1951, **23**, 1611), whereas the C–H stretching fundamentals of methyl and saturated methylene groups occur at lower frequencies. The existence of absorption bands at frequencies greater than 3000 cm.$^{-1}$ in the spectra of all the five complexes we have examined shows that the olefins are not destroyed on complex formation. For example, the spectrum of $K[C_3H_6PtCl_3],H_2O$ has absorption bands at 3068, 3034, and 3010 cm.$^{-1}$, which can be assigned to the three olefinic C–H stretching modes of the co-ordinated olefin.

Since olefins are present in the complexes, and apparently unchanged in any essentiality, we should find absorption bands corresponding to the C=C stretching frequencies, especially when the molecule of the bound olefin is not symmetrical about the double bond. The propylene complexes $K[C_3H_6PtCl_3],H_2O$ and $(C_3H_6PtCl_2)_2$ have a strong absorption band at 1504 cm.$^{-1}$. This absorption is at higher frequencies than the C–H deformation and C–C stretching fundamentals and is very weak in the spectrum of the corresponding ethylene complexes. It is, therefore, assigned to the C=C stretching frequency, lowered by some 143 cm.$^{-1}$ by co-ordination to the metal. This lowering of frequency is about twice that observed in the Raman spectra of silver-ion–olefin complexes (Taufen, Murray, and Cleveland, *J. Amer. Chem. Soc.*, 1941, **63**, 3500) and must be due to the much stronger binding of the olefin to platinum than to silver. The butadiene complex $K_2[C_4H_6(PtCl_3)_2],H_2O$ has a strong absorption band at 1475 cm.$^{-1}$, which cannot be assigned with as much certainty as the absorption at 1504 cm.$^{-1}$ by the propylene complex, but it is possibly a C=C stretching frequency lowered by both conjugation and co-ordination to the metal. In gaseous *trans*-butadiene the corresponding absorption occurs at 1592 cm.$^{-1}$.

Ethylene platinous chloride $(C_2H_4PtCl_2)_2$ has a weak absorption at 1506 cm.$^{-1}$, but in

the spectrum of Zeise's salt, $K[C_2H_4PtCl_3],H_2O$, any absorption in the 1500 cm.$^{-1}$ region of the spectrum was too weak to be observed. The existence of this absorption band, due to the C=C stretching mode, is evidence of the loss of a centre of symmetry by the olefin, but its weakness indicates that the symmetry of the olefin, in so far as it affects the infrared activity of the C=C stretching frequency, has scarcely been altered by co-ordination to the metal atom. The olefin is thus symmetrically co-ordinated about the double bond as required by the structure shown in the Figures.

Anderson (*J.*, 1934, 971) showed that hydrolysis of Zeise's salt at 100° occurred as follows: $[C_2H_4PtCl_3]^- + H_2O = CH_3{\cdot}CHO + 2HCl + Pt + Cl^-$. The absence of symmetrical substituted ethanes led him to suggest that the ethylene was unsymmetrically co-ordinated, but this reaction may proceed through the liberation and hydration of the ethylene to give ethanol which would be oxidised by the platinous salt in the presence of water.

*Dipole Moments.*—In complex compounds where the ligand is bound to the metal by a double bond, the separation of charge usually associated with the co-ordinate link (the σ-bond) will be neutralised to some degree by the drift of electrons from the *d*-orbitals of the metal into vacant orbitals of the ligand in the formation of the π-bond. Unfortunately, it is not possible to measure accurately the dipole moments of complex compounds in solution unless the moments are fairly large, say >3 D. This is because the atom polarisation of co-ordination compounds is large and its value uncertain. Jensen (*Z. anorg. Chem.*, 1936, **229**, 225) found it necessary to assume an atom polarisation ($_AP$) equal to about 20% of the electron polarisation ($_EP$) so that a number of symmetrical *trans*-platinous complexes should have zero moment.

To obtain some idea of the polarity of the olefin–platinum bond, we have examined the electrical asymmetry of such molecules as *trans*-$C_2H_4$,am,$PtCl_2$ (am = amine). Unfortunately, no complexes of this type are known which contain symmetrical amines (*e.g.*, pyridine) and are sufficiently soluble in benzene. It was therefore necessary to use unsymmetrical amines. Assuming that $_AP = 20\%$ of $_EP$, and disregarding its uncertainty in assessing the limits of error, we have found moments of $2{\cdot}35 \pm 0{\cdot}02$ D for *trans*-$C_2H_4$,*p*-$CH_3{\cdot}C_6H_4{\cdot}NH_2$,$PtCl_2$ and $1{\cdot}79 \pm 0{\cdot}03$ D for *trans*-$C_2H_4$,*p*-$Cl{\cdot}C_6H_4{\cdot}NH_2$,$PtCl_2$ in benzene at 25°. These moments (μ) are much smaller than the usual values for molecules containing only one co-ordinate bond, *e.g.*, $C_2H_5{\cdot}NH_2,AlCl_3$, μ = 6·94 D (Nespital, *Z. physikal. Chem.*, 1932, *B*, **16**, 153); $(CH_3)_3N,BCl_3$, μ = 6·23 D; $(CH_3)_3P,BCl_3$, μ = 7·03 D (Phillips, Hunter, and Sutton, *J.*, 1945, 146). Hence, if the N–Pt bond has the high polarity we expect (*ca.* 6 D units) the $C_2H_4$–Pt bond is also highly polar, and it is in the main a co-ordinate rather than a double bond.

Because the moments we have measured are of the order 0—2·5 D, the actual values assumed for $_AP$ have a significant effect on the values of the calculated moments. Thus an estimate of the difference in bond moments, $\mu_{(N-Pt)} - \mu_{(C_2H_4-Pt)}$, and the remaining deductions given in this paragraph are somewhat speculative ($\mu_{(N-Pt)}$ = moment of the N–Pt bond, etc.). On the basis of assumptions set out in the experimental section we estimate the difference to be about 2 D, but our calculations do not determine its sign. We expect, however, on the basis of the structure in the Figures, that $\mu_{(N-Pt)} > \mu_{(C_2H_4-Pt)}$. The value ~2 D receives some support from the moment, 2·81 D, of *trans*-$C_2H_4,NH_3PtCl_3$ measured in dioxan (Shedlovskaya and Syrkin, *Compt. rend. Acad. Sci., U.R.S.S.*, 1947, **55**, 231). Since the moment of the N–Pt bond is unknown but is perhaps of the order 6 D, then the moment of the $C_2H_4$–Pt bond possibly has a value of about 4 D. The low moment thus inferred may be attributed to a weak σ-type bond, to the back-drift of electrons from the platinum to olefin in formation of the π-type bond (cf. Phillips, Hunter, and Sutton, *J.*, 1945, 146), or to some combination of both effects. The low moment is not proof of the existence of a partial double bond between olefin and the metal, but if the lowering is due to double-bond formation then tentatively it appears that the $C_2H_4$–Pt bond has about ⅓ double-bond character. This gives us an approximate upper limit to the double-bond character of the bond.

The $C_2H_4$–Pt bond appears to be fairly strong in platinous chloride complexes containing only one ethylene molecule because no dissociation pressure of ethylene has

been noted over these compounds. Their thermal instability is due to autoreduction to the metal with formation of ethylene dichloride. We consider, therefore, that this, in conjunction with previous evidence for a double $C_2H_4$–Pt bond, renders it highly probable that the low bond moment of about 4 D is due to partial double bonding rather than to a weak σ-type of bond.

*Valency of the Platinum Atom.*—The general chemistry of the olefin complexes indicates that they are square planar platinous complexes in which the platinum atom is formally bivalent, but Hel'man's structure required that the platinum be formally quadrivalent and she presented evidence in support of such valency. We have re-examined this.

The most convincing evidence was provided by the reaction of $K[C_2H_4PtCl_3]$ or $(C_2H_4PtCl_2)_2$ with $CH_3{\cdot}MgI$ to yield $(CH_3)_3PtI$, in which platinum is undoubtedly quadrivalent (Hel'man and Gorushkina, *Doklady Akad. Nauk, S.S.S.R.*, 1947, **57**, 259). Since $CH_3{\cdot}MgI$ is a reducing agent it appeared that the platinum in the original $K[C_2H_4PtCl_3]$ must be quadrivalent. Hel'man used a large excess of methyl iodide, however, to prepare the Grignard reagent. The reaction could thus proceed as follows:

$$K[C_2H_4PtCl_3] + 2CH_3{\cdot}MgI \longrightarrow C_2H_4 + (CH_3)_2Pt + KCl + MgCl_2 + MgI_2$$
$$(CH_3)_2Pt + CH_3I \longrightarrow (CH_3)_3PtI.$$

We repeated her experiment, using $Na_2PtCl_4$ instead of the ethylene complex, and also isolated $(CH_3)_3PtI$: thus its isolation is no evidence that the platinum was originally quadrivalent. These experiments also make it likely that dimethylplatinum exists, although it may only be as a short-lived intermediate.

The second piece of evidence appeared to be weaker. Hel'man and Ryabchikov (*Compt. rend. Acad. Sci., U.R.S.S.*, 1939, **24**, 549) titrated $K[C_2H_4PtCl_3]$, $NH_4[NH_3PtCl_5]$, and $K[NH_3PtCl_3]$ electrometrically with 0·1N-permanganate. Only the last was oxidised, and the initial potentials of the three salts were 650, 660, and 520 mv, respectively. Thus $K[C_2H_4PtCl_3]$ is as resistant to oxidation as the platinic derivative. This was regarded as evidence that the platinum is quadrivalent. However, we know that the redox potentials of complex compounds are very sensitive to a change of ligand. When the co-ordination involves a drift of electrons from *d*-orbitals of the metal into vacant orbitals of the ligand to form a π-bond, the resultant lowering of electron density on the metal atom would reduce the tendency for electrons to be promoted from *d*-orbitals for principal valency formation. It is to be noted that groups of high *trans*-influence, *e.g.*, olefins, CO, $PF_3$, and to a much less extent organic phosphines, arsines, etc., tend to stabilise low valency states of the later transition metals. Exceptions only occur when promotion of electrons from *d*-orbitals into a higher-energy orbital occurs during complex formation, as in the formation of the inner, or lower, orbital complex ion, $Ni[o\text{-}(AsMe_2)_2C_6H_4]_2^{++}$ (Burstall and Nyholm, *J.*, 1952, 3570).

It may be that the redox potentials of a series of exactly analogous inner orbital complex compounds of different ligands with a particular transition metal will serve as a measure of the relative double-bond character of the ligand-to-metal bond; always provided that oxidation occurs by the use of electrons from the *d*-orbitals of the reduced complex for the formation of the additional principal valencies of the oxidised complex.

We find that ethylene platinous chloride in dry acetone is oxidised immediately by a dry acetone solution of permanganate at room temperature; the oxidation is complete when one molecule of oxygen for every molecule of ethylene has been consumed. The products were not identified.

*Halogenation.*—Stilbene dibromide results from the reaction of an excess of bromine with stilbene platinous bromide $[(C_6H_5)_2C_2H_2]_2Pt_2Br_4$ (Kharasch and Ashford, *loc. cit.*), but this is one of the less stable olefin complexes and easy dissociation would account for ready halogenation. Therefore, when we were seeking proof of the ethylidene structure we though it worth while to see if chlorination of ethylene platinous chloride produced any ethylidene dichloride. The reaction with one molecule of chlorine might result in chlorination of the olefin (1) or oxidation of the platinum (2):

$$(C_2H_4)_2Pt_2Cl_4 + 2Cl_2 = 2C_2H_4Cl_2 + 2PtCl_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$(C_2H_4)_2Pt_2Cl_4 + 2Cl_2 = (C_2H_4)_2Pt_2Cl_8 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The theoretical quantity of chlorine, according to these equations, added to a chloroform solution of the ethylene complex gives no precipitate of platinous chloride; thus (2) appears to represent the course of the reaction. No crystalline product was obtained.

When twice the above quantity of chlorine was added to a nitrobenzene solution of ethylene platinous chloride and the solution boiled, ethylene dichloride was the only product derived from the ethylene of the complex.

*Acetylene Complexes.*—It is well known that acetylene forms indefinite brown products with potassium chloroplatinite, probably by the replacement of the active hydrogen atoms. Information as to whether simple disubstituted acetylene platinous complexes exist appears to be lacking. Hel'man, Bakhovetz, and Meilakh (*Compt. rend. Acad. Sci., U.R.S.S.*, 1945, **46**, 105) report that the acetylenic compound $CMe_2(OH)\cdot C{:}C\cdot CMe_2\cdot OH$ (A) forms a complex A,py,$PtCl_2$ analogous to *trans*-$C_2H_4$,py,$PtCl_2$ (py = pyridine); (A) is rather complex and contains two OH groups which might be involved in complex formation. We have, therefore, attempted to obtain complexes of the simple acetylenes $CH_3\cdot C{:}C\cdot CH_3$ and $Ph\cdot C{:}CPh$.

When we attempted to replace ethylene from ethylene platinous chloride in benzene solution by each of these acetylenes separately (cf. Anderson, *J.*, 1936, 1042), a change in the colour of the solution occurred on addition of the acetylene followed by rapid reduction to platinum in each case. A colour change followed by rapid reduction to the metal also occurred when diphenylacetylene was treated with a suspension of platinic chloride in acetic acid (cf. Kharasch and Ashford, *J. Amer. Chem. Soc.*, 1936, **58**, 1733). When but-2-yne (dimethylacetylene) was treated with potassium chloroplatinite in 3% hydrochloric acid (cf. Chernyaev and Hel'man, *Chem. Abs.*, 1938, **32**, 445) no reaction occurred although the substances were kept together in a sealed glass bulb for 9 months. It is evident that platinous complexes of the simple disubstituted acetylenes cannot be isolated by the methods in use for the preparation of olefin complexes. However, the colour changes noted above suggest that some complex formation preceded the reduction when Anderson's and Kharasch and Ashford's methods were tried.

## Experimental

(Microanalyses were made by Mr. W. Brown, of these laboratories.)

None of the published methods of preparation of platinous olefin complexes (see Keller, *Chem. Reviews*, 1941, **28**, 229) is reliable or can be easily adapted to the production of large quantities of the complexes. We have, however, developed from Chernyaev and Hel'man's method of preparing the Zeise type of salts an excellent method of obtaining ethylene and propylene platinous chloride in 80—90% yields.

*Ethylene Platinous Chloride* $(C_2H_4PtCl_2)_2$.—$K_2PtCl_4$ (15 g.) in 3—4% hydrochloric acid solution (75 c.c.) is shaken continuously for 10 days in an atmosphere of ethylene. The solution, which has now changed colour from reddish-brown to golden-orange, yields crystalline potassium ethylene trichloroplatinite monohydrate (7 g.) if it is filtered and cooled in ice-water. To obtain ethylene platinous chloride, however, it is taken to dryness in an evaporating basin in a desiccator over sulphuric acid and sodium hydroxide pellets. The residual mixture of yellow, white (KCl), and a few brown ($K_2PtCl_4$) crystals is extracted with alcohol (200 c.c.) containing concentrated hydrochloric acid (*d* 1·180; 6·2 c.c.), to dissolve the yellow trichloroplatinite. The orange solution is filtered and then taken to dryness under reduced pressure, the temperature being kept below 60°. Almost pure ethylene platinous chloride (10 g.) separates as a rose-coloured powder, decomp. about 165°. The crude product has the same infra-red spectrum as the very pure material described by Chatt and Hart (*Chem. and Ind.*, 1949, 146).

Propylene platinous chloride was prepared as above except that the absorption of propylene by potassium chloroplatinite in 3% hydrochloric acid required 3 weeks. When the mixture of yellow, white, and brown crystals was obtained, a few of the best of the yellow variety were picked out free from the others. These were potassium propylene trichloroplatinite monohydrate, $K[C_3H_6PtCl_3],H_2O$ (Found: C, 9·2; H, 2·0. Calc. for $C_3H_8OCl_3PtK$: C, 9·0; H, 2·0%). The residue, treated as above except that the final distillation of the alcohol was carried out at under 45°, yielded *propylene platinous chloride* as a deep rose powder (decomp.

without melting at about 97°). It was purified by solution in carbon tetrachloride and precipitated with ligroin (b. p. 40—60°), m. p. 98—99·5° (decomp.) (Found: C, 11·7; H, 2·1. $C_6H_{12}Cl_4Pt_2$ requires C, 11·7; H, 2·0%).

*trans-p*-Toluidine-ethylenedichloroplatinum was prepared as previously (Chatt, *J.*, 1949, 3340). trans-p-*Chloroaniline-ethylenedichloroplatinum*, similarly prepared, is less stable than its *p*-toluidine analogue. It was purified by dissolving the crude product (5 g.) in boiling chloroform (50 c.c.), filtering at once, then adding carbon tetrachloride (21 c.c.) and cooling to 0°, giving a recovery of 3·6 g. (58%). It decomposed at 135—142° depending on the rate of heating (Found: C, 22·9; H, 2·5; N, 3·5. $C_8H_{10}NCl_3Pt$ requires C, 22·8; H, 2·4; N, 3·3%).

*Attempts to Prepare Acetylene Complexes.*—(1) *Anderson's method* (loc. cit.). But-2-yne (dimethylacetylene) (0·451 g.) was added to a clear acetone (10 c.c.) solution of $(C_2H_4PtCl_2)_2$ (0·61 g., 0·125 mol.). The solution reddened and started to darken immediately. The acetone was rapidly removed under reduced pressure, leaving a black intractable residue, with an odour reminiscent of mesityl oxide. Diphenylacetylene behaved similarly, except that darkening occurred more slowly.

(2) *Kharasch and Ashford's method* (loc. cit.). Dimethylacetylene (0·433 g.) was added to platinic chloride (1·62 g., 0·6 mol.) in glacial acetic acid (18 c.c.) suspension. On shaking, a very little of the platinic chloride dissolved to give a yellow-orange solution. The mixture was gradually warmed. The platinic chloride became orange without dissolving, and at 35° rapid blackening occurred.

(3) *Chernyaev and Hel'man's method*. $K_2PtCl_4$ (2·63 g.) in 3% HCl solution (70 c.c.) was sealed in a large ampoule with dimethylacetylene (0·38 g., 1·1 mol.) and shaken for 3 weeks. No change in colour or other obvious sign of reaction occurred. After 9 months' storage, the ampoule was opened, and the solution tested for a Zeise type of salt, $K[(CH_3)_2C_2PtCl_3]$. (*a*) The solution (5 c.c.) was treated cautiously with ammonia solution until just alkaline; no rapid

TABLE 1.

| $K[C_2H_4PtCl_3],H_2O$ | $K[C_3H_6PtCl_3],H_2O$ | $K_2[C_4H_6(PtCl_3)_2]$ | $(C_2H_4PtCl_2)_2$ | $(C_3H_6PtCl_2)_2$ |
|---|---|---|---|---|
| * 3460 v.s. | * 3460 v.s. | — | — | — |
| * 3195 w | * 3217 w | — | — | — |
| 3094 v.w. | 3068 m | 3078 m | 3088 m | 3071 w |
| 3081 w | 3034 w | 3070 shoulder | 3072 w | 3039 w |
| 3045 v.w. | 3010 m | 3010 w | 3010 w | 3012 w |
| 3013 w | 2971 shoulder | 2993 v.w. | 2979 v.w. | 2995 shoulder |
| 2985 w | 2965 m | 2959 v.w. | 2956 v.w. | 2988 w |
| — | — | — | — | 2967 v.w. |
| — | — | — | — | 2954 w |
| — | 2911 v.w. | — | — | 2901 v.w. |
| * 1615 s | * 1621 s | — | — | — |
| — | 1504 s | 1473 s | 1506 w | 1504 s |
| — | 1449 s | — | — | 1447 s |
| 1425 s | 1429 s | — | 1428 s | 1431 s |
| — | 1392 m | 1324 m | 1416 m | 1395 s |
| 1300 v.w. | 1365 s | 1236 s | 1236 w | 1361 s |
| 1241 m | 1252 w | 1202 w | 1217 w | 1243 v.w. |
| 1179 w | 1175 m | — | 1175 w | 1171 v.w. |
| 1022 s | 1049 s | 1036 s | 1027 v.s. | 1045 s |
| 1010 s | 1010 s | 1007 s | — | 1021 s |
| 975 v.w. | 990 s | 967 s | 971 v.w. | 995 s |
| — | 932 s | — | — | 929 s |
| — | 899 s | — | — | 898 s |
| — | 800 w | 850 s | — | 877 w |
| — | — | — | — | 820 w |
| — | 809 s | 809 w | 818 m | 807 w |
| 720 m | — | 725 m | — | — |
| — | — | 719 m | — | — |

* These bands are due to water of crystallisation: v.s. = very strong; s = strong; m = medium strength; w = weak; v.w. = very weak.

precipitation of $NH_3,(CH_3)_2C_2,PtCl_2$ took place (cf. $K[C_2H_4PtCl_3] + NH_3$), but only slow separation of platinous ammines (cf. $K_2PtCl_4 + NH_3$). (*b*) The solution (10 c.c.) was slowly treated with $Pt(NH_3)_4Cl_2$ solution until precipitation was complete, leaving a colourless supernatant liquid. The green precipitate (0·53 g.) was analysed: this would contain the acetylene derivative as $Pt(NH_3)_4[(CH_3)_2C_2PtCl_3]_2$ if it had been formed (Found: C, 0·2; H, 2·1; N, 9·5. Calc. for $H_{12}N_4Cl_4Pt$: C, 0·0; H, 2·015; N, 9·3%). The precipitate was, therefore, entirely Magnus salt, $Pt(NH_3)_4PtCl_4$.

*Infra-red Spectra.*—The infra-red spectra between 3500 and 700 cm.$^{-1}$ were measured with a Grubb–Parsons S3A spectrometer. The finely powdered solids were suspended in "Nujol" and, for the regions of CH stretching and deformation frequencies, in hexachlorobutadiene. A lithium fluoride prism was used over the range 3500—2800 cm.$^{-1}$, and a rock-salt prism for the rest of the spectrum. The frequencies of the observed absorption bands are listed in Table 1.

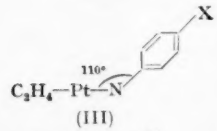
TABLE 2.*

| $10^2\omega$ | $10^2\Delta\varepsilon$ | $10^1\Delta n$ | $-10^2\Delta v$ | ${}_TP$ | ${}_EP$ | ${}_OP$ | $\mu$ |
|---|---|---|---|---|---|---|---|
| *trans*-$C_2H_4$,*p*-$CH_3{\cdot}C_6H_4{\cdot}NH_2$,$PtCl_2$ | | | | | | | |
| 1·021 | 2·09 | — | — | — | — | — | — |
| 1·509 | 3·08 | — | — | — | — | — | — |
| 2·704 | 5·42 | — | 1·91 | — | — | — | — |
| 2·607 | — | 18·7 | — | — | — | — | — |
| 4·118 | — | 30·4 | — | — | — | — | — |
| 4·445 | — | 32·7 | — | 204·6 | 76·7 | 112·6 | 2·35 ± 0·02 |
| *trans*-$C_2H_4$,*p*-$Cl{\cdot}C_6H_4{\cdot}NH_2$,$PtCl_2$ | | | | | | | |
| 1·079 | 1·53 | — | — | — | — | — | — |
| 1·555 | 2·16 | — | — | — | — | — | — |
| 3·092 | 4·13 | — | 2·66 | — | — | — | — |
| 1·131 | — | 7·9 | — | — | — | — | — |
| 1·432 | — | 10·1 | — | — | — | — | — |
| 2·450 | — | 17·1 | — | 158·3 | 77·2 | 65·7 | 1·79 ± 0·03 |

* $\omega$ = weight fraction; $\Delta\varepsilon$ = difference between the dielectric constant of the solution and that of pure benzene; $\Delta n$ = difference in refractive indices; $\Delta v$ = difference in specific volumes; ${}_TP$ = total, ${}_EP$ = electron, and ${}_OP$ = orientation polarisations; $\mu$ = dipole moment.

*Diple Moments.*—These were determined exactly as described by Chatt and Hart (*J.*, 1953, 2363). The remarks regarding the uncertainty in the values due to unknown, but significantly large, atom polarisations apply with equal force to these compounds. The detailed results are given in Table 2. Moments were taken in benzene solution at 25°. The refractive indices are for $\lambda = 6562{\cdot}8$ Å.

To evaluate $\mu_{C-Pt} - \mu_{N-Pt}$, the molecules are assumed to have the shape shown in (III). The two chlorine atoms (not shown) lie on opposite sides of the platinum atom on a line perpendicular to the plane of the paper. It is assumed that the only unbalanced moments in the molecule are $\mu_{(C_2H_4-Pt)}$, $\mu_{(N-Pt)}$, $\mu_{(N-B)}$ and $\mu_{(B-X)}$, (where B = benzene nucleus) and that $\mu_{(B-X)}$ is changed by 1·95 D when Cl is replaced by $CH_3$ [*i.e.*, the difference between $\mu_{(B-Cl)}$ (1·55 D) and $\mu_{(B-CH_3)}$ (0·4 D) in opposite directions]. On the basis of these assumptions, we find $\mu_{(C_2H_4-Pt)} - \mu_{(N-Pt)} = 1{\cdot}9$ D and $\mu_{(N-B)} = 1{\cdot}8$ D with N positive, or $\mu_{(N-Pt)} - \mu_{(C_2H_4-Pt)} = 1{\cdot}9$ D and $\mu_{(N-B)} = 0{\cdot}5$ D with N positive.




(III)

X = $CH_3$ or Cl.

*Reaction of Sodium Chloroplatinite with Methylmagnesium Iodide in Presence of Methyl Iodide.*—The dry, finely powdered sodium salt (5·2 g., 1 mol.) was gradually added to a well-stirred ether (25 c.c.)–benzene (50 c.c.) solution of methylmagnesium iodide containing an excess of methyl iodide (1·5 g. Mg, 4·5 mol.; 15 g. $CH_3I$, 7·75 mol.). The mixture was heated for 1 hr. at 30° and then hydrolysed with ice-water. Crude trimethylplatinic iodide (1·0 g.) was isolated from the benzene layer. Recrystallised from benzene and then from chloroform, the product was obtained as orange-yellow crystals, decomp. 195—200°. It was identified as the dipyridine derivative, m. p. 169—170°; Lile and Menzies (*J.*, 1949, 1168) give 168° (Found: C, 29·9; H, 3·5; Pt, 36·7. Calc. for $C_{13}H_{19}N_2IPt$: C, 29·7; H, 3·6; Pt, 37·1%). The equivalent of 2·5 g. of $Na_2PtCl_4$ was isolated as $Pt(NH_3)_4PtCl_4$ from the aqueous solution. The poor yield of trimethylplatinic iodide and large recovery of platinite is attributed to the very poor solubility of the sodium salt in the ether–benzene mixture.

*Chlorination of Ethylene Platinous Chloride,* $(C_2H_4PtCl_2)_2$.—This chloride (1·2 g., 1 mol.) was dissolved in a minimum of chloroform, and chlorine (2·04 mols.) in carbon tetrachloride (5·7 c.c.) run in with swirling. There was immediate rise in temperature (7°) and the solution became bright reddish-orange. The solvent was now removed at 15—20 mm. pressure. There remained a fairly fluid orange oil, which could not be induced to crystallise. It was very soluble in ethanol and acetone but insoluble in ligroin, benzene, and carbon tetrachloride. It dissolved in aqueous potassium chloride, giving an odour of aldehyde resin. On slight warming, the oil darkened rapidly. On addition of ethylenediamine (2 mols.) to the chloroform solution of the orange product, there was an immediate curdy precipitate which became sticky during

filtration. It was dried at 0·1 mm. pressure, ground, redried, and analysed (Found: C, 13·6; H, 3·7%). An attempt to obtain a crystalline derivative of the orange oil by adding 2 : 2′-dipyridyl (2 mols.) instead of ethylenediamine gave an insoluble oil, stable at 0° but decomposing at room temperature to deposit dipyridyldichloroplatinum.

Chlorine (4·0 mols.) in nitrobenzene (33·5 c.c.) was gradually added to a suspension of ethylene platinous chloride (4·5 g., 1 mol.) in the same solvent (170 c.c.). When half the chlorine had been added the solution was shaken until all the suspension had dissolved to an orange solution and the smell of chlorine was no longer apparent. The remainder of the chlorine solution was now run in, giving a solution smelling strongly of chlorine. Absorption of the second molecule of chlorine was very sluggish. After ½ hr.' standing, the smell of chlorine was still apparent and hydrogen chloride was being slowly evolved. The solution was then distilled up a short fractionating column. Much hydrogen chloride was evolved and the solution blackened. The first few c.c. of distillate were collected, washed with sodium hydrogen carbonate solution, and fractionated, yielding *ca.* 0·5 c.c. of ethylene dichloride, b. p. 82—84°, characterised by conversion into ethylenebis(phenyl sulphide), m. p. 69—70°, alone and mixed with an authentic specimen.

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## 587. *Nucleotides. Part XXII.* Syntheses of* $P^1P^2$*-Diadenosine-5′ and* $P^1P^2$*-Diuridine-5′ Pyrophosphates.*

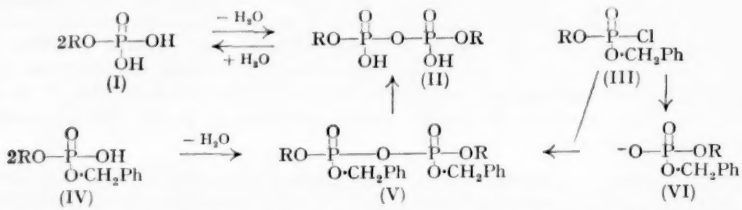
By S. M. H. Christie, D. T. Elmore, G. W. Kenner, A. R. Todd, and F. J. Weymouth.

Methods suitable for the preparation of $P^1P^2$-diesters (II) of pyrophosphoric acid, developed in earlier model experiments, have been applied to the synthesis of $P^1P^2$-diadenosine-5′ pyrophosphate and $P^1P^2$-diuridine-5′ pyrophosphate. These syntheses demonstrate the applicability of the methods in the nucleotide field and indicate the feasibility of synthesis of dinucleotide coenzymes. Four different types of pyrophosphate synthesis have been used and their relative merits are discussed from the standpoint of ultimate application to the synthesis of such natural coenzymes as flavin–adenine dinucleotide and uridine–diphosphate–glucose. The synthetic pyrophosphates are hydrolysed to the parent nucleosides by the crude venoms of Russell's viper and diamond-back rattlesnake.

Naturally occurring nucleotide derivatives, which exercise coenzyme function, fall into two structural groups. The first group, which includes such substances as adenosine diphosphate and adenosine triphosphate, consists of monoesters of pyrophosphoric and triphosphoric acid. The synthesis of such nucleotides has been described in earlier papers of this series (Part I, *J.*, 1947, 648; Part II, *J.*, 1949, 582; Part IV, *J.*, 1949, 2487; Part XV, *J.*, 1952, 3665; Part XVII, *J.*, 1952, 3675). The second group, whose members are unsymmetrical $P^1P^2$-diesters of pyrophosphoric acid, is of considerable importance since it includes such coenzymes as flavin–adenine dinucleotide (FAD), uridine–diphosphate–glucose (UDPG), coenzymes I and II (DPN and TPN), and coenzyme A. The synthesis of such substances presents many difficulties, but during recent years we have developed, in model experiments, methods which should be applicable to this end, and which have been described partly in earlier papers of this series and partly in our cognate series entitled "Studies on Phosphorylation" (Parts I—XI, *J.*, 1945—1953). The present paper describes experiments in which we have tested their practical utility in the nucleotide field by the synthesis of $P^1P^2$-diadenosine-5′ pyrophosphate (II; R = adenosine-5′ residue) and $P^1P^2$-diuridine-5′ pyrophosphate (II; R = uridine-5′ residue).

* Part XXI, *J.*, 1953, 2040.

This task was relatively easy, owing to the favourable solubilities of the intermediates and the symmetry and stability of the products, but its successful completion demonstrates the feasibility of synthesising the natural dinucleotide coenzymes. In all, four distinct methods have been employed, the pyrophosphate being formed by the use of carbodiimides, by exchange reactions using trifluoroacetic anhydride or tetraphenyl pyrophosphate, and by employing nucleoside phosphorochloridates (chlorophosphonates). The use of each method will be described in turn before discussing their relative potentialities for coenzyme synthesis.




The most direct method of preparing diesters of pyrophosphoric acid is by condensation of two molecules of a monoester of phosphoric acid (I) by means of di*cyclo*hexyl carbodiimide (Khorana and Todd, *J.*, 1953, 2257), which has the advantage over other dehydrating agents of attacking acidic groups preferentially. It is not, however, necessary to use free phosphoric acids, for tetrabenzyl pyrophosphate is formed by reaction between carbodiimides and pyridinium, although not triethylammonium, dibenzyl phosphate. Some nucleotide coenzymes, *e.g.*, uridine–diphosphate–glucose, are very labile to acids, and therefore our model experiments were carried out with pyridinium uridine-5′ hydrogen phosphate. When a slight excess of di*cyclo*hexyl carbodi-imide was added to a solution of the pyridinium salt in dimethylformamide, di*cyclo*hexylurea rapidly crystallised; paper chromatography then showed that 60% of the uridine-5′ phosphate had been converted into a new substance with the same $R_F$ as uridine-5′ pyrophosphate and as uridine–diphosphate–glucose. By using a large excess of the carbodi-imide, almost all the uridine-5′ phosphate could be brought into reaction, but some of it was converted into yet another material, probably of higher molecular weight. Formation of this by-product was avoided when pyridine was used as solvent, and the small amount of unchanged starting material was removed by repeated precipitation of the pyridinium salt from aqueous solution with acetone. The crystalline product was shown by analysis and electrometric titration to be monopyridinium $P^1P^2$-diuridine-5′ pyrophosphate.

The synthesis of diadenosine-5′ pyrophosphate was also achieved in a direct fashion, but as an unexpected result of another investigation. Brown, Magrath, and Todd (*J.*, 1952, 2708) showed that uridylic and cytidylic acids can be partially esterified with simple alcohols by means of trifluoroacetic anhydride. This result offered a possible route to dinucleoside esters of phosphoric acid, and this was tested in an attempt to synthesise the already known adenosine-5′ uridine-5′ phosphate (Elmore and Todd, *J.*, 1952, 3681). A solution of 2′ : 3′-*O-iso*propylideneuridine in dioxan was added to the reaction mixture of adenosine-5′ phosphate with trifluoroacetic anhydride. Paper chromatography of the product, after ethanolysis of trifluoroacetyl groups, revealed the presence of only one new substance and this did not contain a uracil residue. Moreover, repeated applications of trifluoroacetic anhydride to adenylic acid alone produced the same new substance. The possibility that it was adenosine-5′ ethyl phosphate, formed during the ethanolysis, was disproved by substitution of benzyl for ethyl alcohol; the $R_F$ of the product was unchanged and quite distinct from that of adenosine-5′ benzyl phosphate (Baddiley and Todd, *J.*, 1947, 648). Anion-exchange chromatography with formic acid elution gave an efficient separation of unchanged adenylic acid from the new material. The analysis of the free acid and the results of electrometric and periodate titrations left no doubt that it was $P^1P^2$-diadenosine-5′ pyrophosphate (II; R = adenosine-5′ residue).

The above two direct syntheses represent a departure from our usual practice, which

has been to build up completely esterified nucleotides containing protective benzyl groups, which are removed in the final stages. The alternative synthesis of $P^1P^2$-diuridine-5′ pyrophosphate now to be described is derived from our earlier studies, in particular the preparation of benzyl 2′ : 3′-*O*-*iso*propylideneuridine-5′ phosphorochloridate (chlorophosphonate) (III; R = 2′ : 3′-*O*-*iso*propylideneuridine-5′ residue) (Corby, Kenner, and Todd, *J.*, 1952, 3669; Kenner, Todd, and Weymouth, *J.*, 1952, 3675). Toy (*J. Amer. Chem. Soc.*, 1948, **70**, 3882) has shown that phosphorochloridates can be converted into symmetrical tetraesters of pyrophosphoric acid in two ways, both of which have been used successfully in the present instance. The simpler method is to add water, in small excess, and then one equivalent of base to a solution of the phosphorochloridate in methyl cyanide. The pyrophosphate (V) is then formed by reaction between the anion (VI), derived from hydrolysis of the phosphorochloridate, and a further quantity of the chloride. The alternative and, in our experience, slightly superior procedure is to carry out the two steps separately. The further stage of removing the two benzyl groups could be accomplished by heating the pyrophosphate (V) with lithium chloride in ethoxyethanol (Anand, Clark, Hall, and Todd, *J.*, 1952, 3665), but the product contained uridine-5′ phosphate (I; R = uridine-5′ residue). This could only have arisen from the debenzylated pyrophosphate (II), since diesters (IV) of phosphoric acid are not attacked by lithium chloride (Clark and Todd, *J.*, 1950, 2031). In other words, hot ethoxyethanol causes appreciable cleavage of the pyrophosphate link in addition to partial removal of *iso*propylidene residues. We therefore turned to use of the thiocyanate anion for debenzylation in non-hydroxylic solvents (Morrison and Atherton, B.P. 675,779). Two hours' reaction with potassium thiocyanate in boiling methyl cyanide was sufficient to cause complete debenzylation without untoward side-reactions. The two *iso*propylidene groups were then removed with dilute hydrochloric acid. Final purification was achieved by anion-exchange chromatography with hydrochloric acid elution. The 0·1N-acid fractions contained the pyrophosphate (II; R = uridine-5′ residue), which was recovered as its dilithium salt by precipitation with acetone after neutralisation of the concentrated liquors with lithium hydroxide.

Fully esterified pyrophosphates (V) can also be prepared by exchange reactions between diesters of phosphoric acid (IV) and a suitable reactive pyrophosphate or other anhydride (Corby, Kenner, and Todd, *J.*, 1952, 1234). Tetraphenyl pyrophosphate was allowed to react with monobenzyl triethylammonium 2′ : 3′-*O*-*iso*propylideneuridine-5′ phosphate in methyl cyanide solution. Successive treatment of the resultant mixture with potassium thiocyanate and dilute hydrochloric acid afforded $P^1P^2$-diuridine-5′ pyrophosphate, but in only moderate yield. It was even lower in a similar experiment starting with the corresponding potassium salt and trifluoroacetic anhydride in dimethylformamide. These exchange reactions with nucleotides were thus much less successful than those with simple model compounds, possibly owing to the greater difficulty encountered in excluding moisture.

Syntheses of the natural pyrophosphate coenzymes present three major difficulties in addition to those encountered in the present work. Nevertheless it is possible to draw some conclusions about the relative utility of the four types of synthetic method described above. The coenzymes are not symmetrical esters of type (II), but have two different attached groups. Only the method using reaction between a phosphorochloridate (III) and an anion (VI) leads to such structures in other than a random way. It gave a very satisfactory yield (48%) of pure $P^1P^2$-diuridine-5′ pyrophosphate, but suffers from being limited to inert solvents such as benzene or methyl cyanide. Intermediates in the synthesis of coenzymes containing quaternary nicotinamide or riboflavin residues are not likely to be freely soluble even in methyl cyanide. To some extent this difficulty can be overcome by protection of polar groups with hydrophobic residues, but subsequent removal of these protecting groups is hindered by instability of the coenzymes, the third obstacle. For instance, flavin–adenine dinucleotide is very labile to alkali (Forrest and Todd, *J.*, 1950, 3295) and uridine–diphosphate–glucose to acid (Caputto, Leloir, Cardini, and Paladini, *J. Biol. Chem.*, 1950, **184**, 333). The carbodi-imide method is superior in these last two respects, since no protecting groups are necessary and the solvent may be pyridine

or dimethylformamide. The conversion of uridine-5′ phosphate into the pyrophosphate was high (60%), but the yield of an unsymmetrical ester would presumably be much lower. The other two types of synthesis described offer less satisfactory solutions of these problems and the yields obtained were much lower.

The following observations on the synthetic $P^1P^2$-diadenosine-5′ and $P^1P^2$-diuridine-5′ pyrophosphates are worthy of note. To acid and, particularly, alkali, both pyrophosphates were rather more stable than we had expected. For instance, the uridine compound suffered only 4% decomposition in 0·1N-sodium hydroxide during 80 min. at 100°. Both substances (II; R = adenosine-5′ or uridine-5′ residues) were hydrolysed to the nucleosides by the crude venoms of Russell's viper (*Vipera russelli*) and diamond-back rattlesnake (*Crotalus adamanteus*). This is explicable if the venoms contain a non-specific pyrophosphatase capable of degrading even these unnatural substances to the simple mononucleotides, which would then be attacked by the well-known 5′-nucleotidase present in the venoms. In addition to adenosine-5′ and uridine-5′ phosphates, the corresponding nucleoside-5′ monoesters of pyrophosphoric acid were also hydrolysed to the nucleosides. The cleavage of cozymase by snake venoms has, of course, already been reported (Chain, *Biochem. J.*, 1939, **33**, 407; Zeller and Epperson, cited in Sumner and Myrbäck, "The Enzymes," Academic Press, New York, 1951, Vol. I, Part 2, p. 1008).

## Experimental

*Barium Uridine-5′ Hydrogen Phosphate* [with Dr. J. Davoll].—A solution of 5′-deoxy-5′-iodo-2′ : 3′-*O-iso*propylideneuridine (4·0 g.; Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113) in dry benzene (50 c.c.) was refluxed for 90 min. with silver dibenzyl phosphate (4·0 g.). The solution was filtered and washed with water, sodium thiosulphate solution, sodium hydrogen carbonate solution, and again water. Evaporation of the dried ($Na_2SO_4$) benzene left a colourless resin (5·6 g.), which was dissolved in 50% aqueous ethanol (200 c.c.) and shaken for 15 hr. with hydrogen (1 atm.) and a mixture of palladous oxide (0·04 g.) and 10% palladised charcoal (0·04 g.). *Barium uridine-5′ hydrogen phosphate* (3·69 g., 81%) was precipitated by addition of ethanol (120 c.c.) to the filtered solution after it had been concentrated to 25 c.c. and neutralised (pH 5—6) with aqueous barium hydroxide [Found, in air-dried material: C, 24·2; H, 3·7; N, 6·2. $(C_9H_{12}O_9N_2P)_2Ba,6H_2O$ requires C, 24·1; H, 4·0; N, 6·2%].

*Pyridinium* $P^1P^2$-*Diuridine-5′ Hydrogen Pyrophosphate* (*Carbodi-imide Method*).—An aqueous M-solution of pyridinium sulphate was added drop by drop to a solution of barium uridine-5′ hydrogen phosphate (1·0 g.) in water (20 c.c.) until no further precipitate was formed. The filtered solution was evaporated, dissolved in dimethylformamide, and re-evaporated, giving the pyridinium salt as a stable glass. This was dissolved in dry pyridine (10 c.c.) and treated with a solution of di*cyclo*hexyl carbodi-imide (0·30 g.; Schmidt, Hitzler, and Lahde, *Ber.*, 1938, **71**, 1933) in pyridine (3 c.c.). After a few min. an oil began to separate and after 15 min. it contained crystals of di*cyclo*hexylurea. Water (5 c.c.) was then added and the mixture kept for 1 hr. The filtered solution was concentrated to 5 c.c. and poured into acetone (45 c.c.). The precipitated oil (0·60 g.) was collected by centrifugation and twice reprecipitated from aqueous acetone; it then started to crystallise. By slow crystallisation from aqueous acetone the *monopyridinium* salt (0·053 g.) was obtained as rosettes of flat needles, m. p. 216—218° (corr.; decomp.) (Found, in material dried at 50°: C, 38·3; H, 4·1; N, 9·9; P, 8·7. $C_{23}H_{29}O_{17}N_5P_2,\frac{1}{2}H_2O$ requires C, 38·4; H, 4·2; N, 9·75; P, 8·6%). Neither free nor labile orthophosphate was present and the substance consumed 2·07 mols. of sodium metaperiodate during 18 hr. at 20°. Ultra-violet absorption in 0·01N-HCl: max. 257—258 mμ (ε 23,700), min. 230—231 mμ (ε 7500). A solution of 4·35 mg. in 1 c.c. of water had pH 2·56 and, on back-titration from pH 10, showed a break in the curve at a mean pH of 5·6 requiring 0·84 equiv. of acid, corresponding to re-formation of the pyridinium ion (p$K$ 5·3) (secondary phosphoryl dissociations have p$K$ *ca.* 6·8).

A greater yield of this crystalline monopyridinium salt could probably have been obtained, for about 90% of the nucleotidic material in the original oil was the desired pyrophosphate, the remainder being uridine-5′ phosphate. A four-fold increase in the proportion of carbodi-imide (to 5 equivs.) caused conversion of 85% of the phosphate into pyrophosphate.

$P^1P^2$-*Diadenosine-5′ Pyrophosphate* (*Trifluoroacetic Anhydride Method*).—Adenosine-5′ phosphate (0·768 g.) was kept overnight with trifluoroacetic anhydride (5 c.c.). Evaporation under reduced pressure then left a frothy glass, which was treated in the same way with two

further portions of anhydride (4 and 3 c.c.). The final glass was kept for a short time with ethanol (5 c.c.) before evaporation and dissolution in dilute aqueous ammonia. The solution (pH 8) was put on a column (11 × 2·5 cm.) of Dowex-2 resin (250—500 mesh; formate cycle). Unchanged adenosine-5′ phosphate was eluted by 0·1N-formic acid, and the product by 0·5N-formic acid from which it was recovered by evaporation under reduced pressure and freeze-drying. When the residue (0·143 g., 17%) was dissolved in water (1 c.c.), P¹P²-*diadenosine-5′ pyrophosphate* separated rapidly as a dense, amorphous, rather insoluble solid (Found: C, 32·2; H, 4·8; N, 18·7; P, 8·4. $C_{20}H_{26}O_{13}N_{10}P_2,4H_2O$ requires C, 32·1; H, 4·6; N, 18·7; P, 8·3%). It could not be crystallised but gave a single spot on paper chromatography in *n*-butanol–acetic acid–water (5 : 2 : 3; $R_F = 0·09$) and in *iso*propanol–1% aqueous ammonium sulphate (75 : 25; $R_F = 0·06$). Ultra-violet absorption: (1) in 0·01N-HCl: max. 257—259 mμ (ε 27,700), min. 230—231 mμ (ε 7300); (2) in 0·01N-NaOH: max. 259—260 mμ (ε 24,600), min. 229 mμ (ε 5100). In 16 hr. at 20° the substance consumed 2·25 mols. of 0·025M-sodium metaperiodate (calc. on mol. wt. 748). On potentiometric titration of a solution of 4·3 mg. in water (1 c.c.) with 0·05N-sulphuric acid from pH 8 no group was detected in the range to pH 5 characteristic of secondary phosphoryl. The pyrophosphate was stable to 0·5N-sodium hydroxide at room temperature overnight, but was slowly hydrolysed by the same reagent at 100°, adenine being the only product detected in ultra-violet light on a paper chromatogram. On the other hand hydrolysis to adenosine-5′ phosphate and adenine was practically complete after 1 hr. in 0·1N-hydrochloric acid at 100°.

*Potassium Benzyl 2′ : 3′-O-iso*Propylideneuridine-5′ *Phosphate*.—Benzene (20 c.c.) was refluxed for 2½ hr. together with 5′-deoxy-5′-iodo-2′ : 3′-*O-iso*propylideneuridine (1·17 g.), silver dibenzyl phosphate (1·17 g.), and anhydrous calcium sulphate (1 g.). The filtered solution was evaporated to a colourless resin, which was treated with potassium thiocyanate (0·43 g.) in boiling methyl cyanide (10 c.c.) for 2 hr. The colourless *potassium benzyl 2′ : 3′-O-iso-propylideneuridine-5′ phosphate* (0·96 g.), m. p. 288° (corr.; decomp.), which began to separate after 1 hr., was filtered from the cold solution (Found: in material dried at 80°: C, 46·2; H, 4·3; N, 5·9. $C_{19}H_{22}O_{19}N_2PK$ requires C, 46·4; H, 4·5; N, 5·7%). The triethylammonium salt was prepared from this potassium salt by acidifying its aqueous solution with dilute hydrochloric acid and evaporating the dried ($Na_2SO_4$) chloroform extract of the free acid with excess of triethylamine.

*Ammonium Benzyl Phosphite*.—This substance, used in the preparation of benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphite, is more conveniently prepared by the following method (personal communication from Dr. F. R. Atherton) than by that previously published. A solution of dibenzyl phosphite (25 g.) and dried ammonium thiocyanate (12·5 g.) in ethyl methyl ketone (85 c.c.) is refluxed for 2 hr. On addition of ethyl acetate (25 c.c.) and cooling, the ammonium monobenzyl phosphite (12 g.) crystallises in colourless needles, m. p. 153—155° (corr.), and is washed with ethyl acetate.

*Dilithium* P¹P²-*Diuridine-5′ Pyrophosphate* (*Phosphorochloridate Method*).—(*a*) A solution of benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphite (0·869 g.) and *N*-chlorosuccinimide (0·270 g.) in benzene (6 c.c.) and methyl cyanide (0·5 c.c.) was kept for 1½ hr. at 20° before addition to a solution of triethylammonium benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate (1·10 g.) in benzene (20 c.c.) and methyl cyanide (4 c.c.). Triethylammonium chloride began to separate after a few min. and was filtered off (0·110 g.) after 1 hr. The filtrate was evaporated to dryness and then heated for 2 hr. with potassium thiocyanate (0·80 g.) in boiling methyl cyanide (25 c.c.). The precipitated bright yellow solid was dissolved as completely as possible in N/7-hydrochloric acid (15 c.c.) and kept overnight at 20°. The solution was filtered and brought to pH 3·5 with barium hydroxide solution. The barium salt of the product (1·16 g.) was then precipitated as a white powder by the addition of barium bromide (0·60 g.) and ethanol (2 vols.). Paper chromatography in *iso*propanol–1% ammonium sulphate solution (67 : 33), followed by elution of the spots, showed that the ultra-violet absorption at 260 mμ was distributed amongst the components as follows: *P¹P²*-diuridine-5′ pyrophosphate ($R_F$ 0·19) 83%, uridine-5′ phosphate ($R_F$ 0·35) 11%, and unidentified material ($R_F$ 0·10) 6%. The solution of the crude barium salt (1·05 g.) in water (20 c.c.) was brought to pH 8 with aqueous ammonia and then passed slowly through a column (8 × 2·5 cm.) of Dowex-2 (previously cycled three times with 0·5N-sodium hydroxide and N-hydrochloric acid). After being washed with demineralised water (300 c.c.) the column was developed by successive elution with 0·005N-hydrochloric acid (240 c.c.), 0·01N-acid (400 c.c.), 0·025N-acid (400 c.c.), 0·05N-acid (400 c.c.), 0·1N-acid (600 c.c.), and 0·3N-acid (300 c.c.). In all 200 fractions (11·7 c.c. each) were collected, giving sharp separation of the uridine-5′ phosphate, the pyrophosphate, and the unidentified material, which were eluted by

0·025N-, 0·1N-, and 0·3N-hydrochloric acid respectively. Fractions 110—180, containing the pyrophosphate, were combined, neutralised (pH 7) with lithium hydroxide, and concentrated to 40 c.c. Addition of acetone (200 c.c.) then precipitated an oil, which solidified when stirred with ethanol. The solid was redissolved in water (8 c.c.), and the *dilithium* P¹P²-*diuridine-5′ pyrophosphate* (0·57 g.) reprecipitated as an oil by acetone (200 c.c.) and solidified by stirring it with ethanol (Found, in material dried at 100°: C, 33·4; H, 3·8; N, 8·5; P, 9·7. $C_{18}H_{22}O_{17}N_4P_2Li_2,\frac{1}{2}H_2O$ requires C, 33·2; H, 3·5; N, 8·6; P, 9·5%). The hygroscopic solid gave no turbidity with silver nitrate solution, and contained neither free nor labile orthophosphate. It consumed 1·92 mols. of sodium metaperiodate during 18 hr. at 20°. Ultraviolet absorption in $H_2O$: max. 261 mμ (ε 17,300), min. 231 mμ (ε 4300) (calc. on mol. wt. 651). Electrometric titration with 0·05N-sulphuric acid of a solution of 3·3 mg. in water (1 c.c.), made alkaline with 0·1N-sodium hydroxide, showed no titratable group between pH 8·5 and pH 4. Lability of the pyrophosphate to alkaline and acid hydrolysis was studied by treating 5-mg. portions with 0·2 c.c. of reagent, and examining the solutions by paper chromatography in *iso*propanol–1% aqueous ammonium sulphate solution (67 : 33) after suitable reaction periods. The extent of decomposition was then determined by elution of the spots produced, and measurement of the relative optical densities at 260 mμ. In sodium hydroxide no decomposition was detected after 7 hr. at 100° in 0·001N-, 2% after 7 hr. at 100° in 0·01N-, 4·2% after 1⅓ hr. at 100° and 1·4% after 120 hr. at 23° in 0·1N-alkali. In hydrochloric acid decomposition occurred to the extent of 1% after 3½ hr. at 100° in 0·001N-, 2·8% after 2 hr. at 100° in 0·01N-, 47·4% after 1½ hr. at 100° and 4·7% after 180 hr. at 23° in 0·1N-acid.

(*b*) A mixture of benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphite (0·445 g.) and *N*-chlorosuccinimide (0·146 g.) in benzene (5 c.c.) was kept at room temperature for 2 hr. A solution of water (20 mg.) in methyl cyanide (0·5 c.c.) was then added to the mixture, which was stirred vigorously for 30 min. after slow addition of triethylamine (0·15 c.c.). The solvent was evaporated and replaced by methyl cyanide (10 c.c.). The solution was now refluxed for 2 hr. with potassium thiocyanate (0·165 g.); potassium chloride separated and caused severe bumping. The cooled mixture was diluted to 50 c.c. with acetone, and the mixed potassium salts (0·423 g.) were centrifuged off. The solution of these salts in N/7-hydrochloric acid (12 c.c.) was kept overnight at 20° and then neutralised (pH 8) with aqueous barium hydroxide. Addition of barium bromide (0·1 g.) and ethanol (4 vols.) then precipitated barium *P*¹*P*²-diuridine-5′ pyrophosphate (0·273 g.), which was shown by paper chromatography to be about 85% pure; reprecipitation of the barium salt from water (2 c.c.) at pH 4 by addition of ethanol gave a 75% recovery of material substantially free from uridine-5′ phosphate, but still containing an unidentified impurity. Several similar runs were made under varied conditions, and the results showed that the proportion of water was not critical between the theoretical and a 200% excess (100% excess was used above), that the dibenzyl di-2′ : 3′-*O-iso*propylideneuridine-5′ pyrophosphate could be washed with sodium hydrogen carbonate solution and water with a loss of some 30%, and that debenzylation by lithium chloride in ethoxyethanol during 2 hr. at 100° was unsatisfactory owing to considerable cleavage of the pyrophosphate link.

*Dilithium* P¹P²-*Diuridine-5′ Pyrophosphate* (*Trifluoroacetic Anhydride Method*).—Trifluoroacetic anhydride (0·105 c.c.) was added to a suspension of potassium monobenzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate in dimethylformamide (8 c.c.). After 15 min. any unchanged anhydride was removed under reduced pressure and potassium thiocyanate (0·39 g.) was added. The solution was kept at 70—80° for 2 hr. before being poured into dry ether (200 c.c.). The gelatinous precipitate was collected by centrifugation and dissolved in N/7-hydrochloric acid (7 c.c.). The next day the mixed barium salts of uridine-5′ phosphate and *P*¹*P*²-diuridine-5′ pyrophosphate were precipitated by successive additions of barium hydroxide solution (to pH 3·5), barium bromide (0·30 g.), and ethanol (3 vols.). The solution of the salts in water (4 c.c.) was brought to pH 8 by aqueous ammonia before being put on a column (2 × 1·5 cm.) of Dowex-2 resin which was eluted successively with 200-c.c. portions of water, 0·025N-, 0·05N-, and 0·1N-hydrochloric acid. The second major component was in 160 c.c. of the last eluate, the optical density at 260 mμ (5·94) corresponding to the presence of 25 mg. of *P*¹*P*²-diuridine-5′ pyrophosphate. The lithium salt (15 mg.), obtained by neutralisation to pH 7 with lithium hydroxide, evaporation to small bulk, and precipitation by ethanol, contained less than 1% of uridine-5′ phosphate, as detected by paper chromatography.

*Barium* P¹P²-*Diuridine-5′ Pyrophosphate* (*Pyrophosphate Exchange Method*).—A solution of triethylammonium benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate (1·03 g.) in dry benzene (5 c.c.) was evaporated to a gum, which was redissolved in dry methyl cyanide (10 c.c.). Tetraphenyl pyrophosphate (0·508 g.) was added and the solution was kept at 20° for 1 hr. It was

then boiled for 3 hr. with potassium thiocyanate (0·348 g.). The precipitated solid was collected and dissolved in N/7-hydrochloric acid (7 c.c.). The solution was kept at 20° for 15 hr. before addition of barium hydroxide solution (to pH 4) and barium bromide (0·6 g.). After filtration 2 vols. of ethanol were added to the filtrate, and the flocculent precipitate (0·444 g.) collected. It was redissolved in water (2 c.c.) and reprecipitated by an equal vol. of methanol in presence of barium bromide at pH 3·5. Two further repetitions of the process afforded the pure *barium* salt (0·120 g.) (Found, in material dried at 50°: C, 27·5; H, 3·6; N, 6·8; P, 7·8. $C_{18}H_{22}O_{17}N_4P_2Ba,H_2O$ requires C, 27·6; H, 3·1; N, 7·1; P, 7·9%). It ran as a single spot on a paper chromatogram in *n*-butanol : acetic acid : water (50 : 20 : 30) at the same speed as the authentic dilithium salt ($R_P$ 0·13). Measurements of optical densities at 260 mμ of eluates of appropriate areas of the paper showed the amount of uridine-5′ phosphate contaminant to be less than 0·5%.

*Action of Snake Venoms on Synthetic Phosphates and Pyrophosphates.*—Aqueous solutions of the venom of Russell's viper (*Vipera russelli*) and diamond-back rattlesnake (*Crotalus adamanteus*) were incubated with the following substances in 0·25M-glycine–ammonia buffer (pH 9) at 37° overnight: adenosine-5′ phosphate, adenosine-5′ pyrophosphate, $P^1P^2$-di-adenosine-5′ pyrophosphate, uridine-5′ phosphate, uridine-5′ pyrophosphate, $P^1P^2$-diuridine-5′ pyrophosphate. In every case complete degradation to the parent nucleoside (detected by paper chromatography) occurred.

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## 588. *The Measurement of Optical Rotatory Dispersion.* (+)-*Octan-2-ol.*

By M. K. Hargreaves.

The methods available for the investigation of the relation between optical rotatory power and wave-length are reviewed. A photoelectric device for the control of an iron arc is described, by which the scope of Lowry's ultra-violet polarimeter is increased.

As a first step in an investigation of the relation between optical rotatory power and molecular configuration, the optical rotatory dispersion of (+)-octan-2-ol has been re-examined in greater detail than hitherto, both in the homogeneous state and in solution in *n*-heptane. The dispersion curve in the ultra-violet region shows no marked deviation from the simple hyperbolic form, but the dispersion ratio of the *n*-heptane solution clearly indicates complexity.

It is now generally realised that work on optical rotatory dispersion should include measurements in the ultra-violet region of the spectrum and that it is dangerous to draw conclusions from measurements of optical rotatory power made under differing conditions at only one wave-length. The methods hitherto used for this purpose are briefly as follows.

The photographic method of Cotton and Descamps (*Compt. rend.*, 1926, **182**, 22) and the photoelectric method of Bruhat and Chatelain (*ibid.*, 1932, **195**, 462) have not found favour; Brode (*J. Opt. Soc. Amer.*, 1951, **41**, 987) and Broser and Lautsch (*Z. Naturforsch.*, 1951, **6**, *b*, 369) have recently devised other photoelectric methods, the latter authors employing a photo-multiplier, but insufficient data are available for an evaluation of these methods for a determination of the rotatory power of organic liquids in the ultra-violet region. Two new techniques which may be expected to have application in the study of optical-rotatory dispersion are as follows.

*The rotating-sector method.* The chief disadvantage of the photoelectric method in the ultra-violet region is that at the extinction point the light passing through the optical

system is of very low intensity, and the amplitude of the electrical response to the photo-cell is of the order of the " background " noise of the amplifier. This problem has now been virtually surmounted for many purposes, *e.g.*, in electron-diffraction measurements (Roth, *Ann. Reports Phys. Chem.*, 1951, **2**, 218), by application of various modifications of the rotating-sector technique. Since the accuracy is proportional to the exposure a number of exposures at different settings of the analyser would be required, the advantages of this method might not be as great in this as in other work.

*The image converter.* This device has an obvious application to polarimetry, both in the infra-red and in the ultra-violet region, if it should be capable of the necessary accuracy in the reproduction of the image intensity. Unfortunately, the commercial instruments available for conversion of an ultra-violet into a visible image show little gain in brilliance over direct vision with a fluorescent screen (Messrs. Mullard, Ltd., personal communication). There is, therefore, little point in considering the accuracy of the representation of the image intensity.

Lowry and Coode-Adams's method (*Phil. Trans.*, 1927, **226**, *A*, 391) seems to provide the best available combination of accuracy with simplicity of the optical working parts. Its chief disadvantage is that it is extremely tedious, the apparatus requiring constant attention to ensure that the fields of the polarimeter are evenly illuminated. The following development of a photo-electronic device to control the iron arc largely overcomes this disadvantage.

## Experimental

*Apparatus.—Polarimeter.* Basically, the apparatus is similar to that of Lowry and Coode-Adams (*loc. cit.*). Instead of the large metal scale of the earlier instrument, there is a glass scale divided to 0·005° whose image can be projected on to the photographic plate of the spectrograph. However, the deviation of the beam from the objective ($L_2$, Fig. 1) is such that for large rotations the spectrograph must be moved so as to continue to receive the image of the polariser on the slit ($S$). In this case the necessity for refocusing the image of the scale on the plate offsets any advantage accruing from the recording of the reading. The optic of the polarimeter consists of standard Hilger Foucault prisms, with a 9″-focus quartz condenser ($L_1$, Fig. 1) and a 15″ quartz–fluorite achromatic projection lens of 1″ aperture ($L_2$). The quartz wedge supplied with the analyser was found to increase the deviation of the beam, and was discarded.

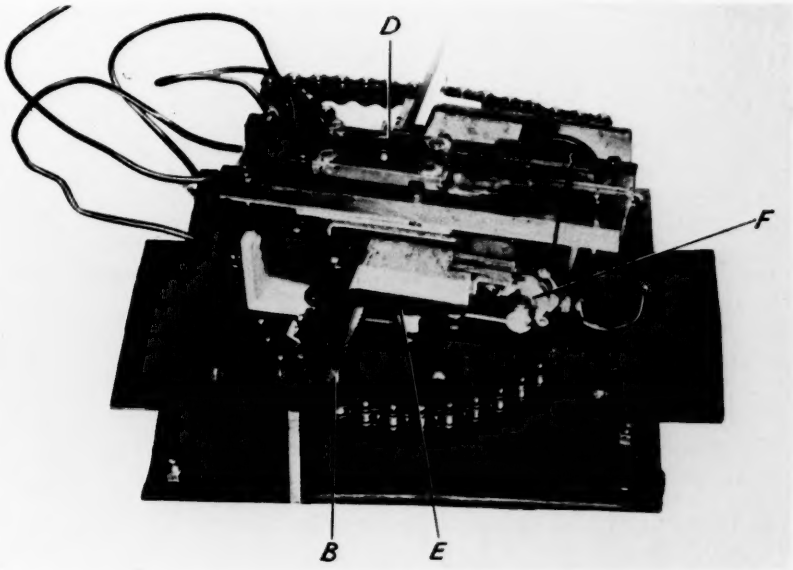
*Polarimeter tubes.* These were of fused silica with integral end-plates and detachable brass jackets. The temperature was controlled to $<0{\cdot}1°$ at 25° and to 0·2° at the higher temperatures. A small correction is required for the rotation due to imperfections in some of the end-plates.

*Arc.* An iron arc is used as a high-intensity source of light and to provide an accurate wave-length scale. Its disadvantages are its inconstancy and unevenness. With substances of low dispersive power the latter can cause considerable error, which can be seen clearly by the use of a three-field polarimeter, particularly when readings are taken to determine the zero of the instrument, there being no dispersion.

A new photoelectric method of arc control (Figs. 1 and 2, and Plate) ensures that the beam of light passes centrally through the optical system of the polarimeter, and thus that the three fields of the polarimeter are evenly illuminated. A circuit diagram of the photo-cell amplifier is given in Fig. 2, and the Plate shows the mechanism by which the arc is moved to the correct position.

The control system only operates when light falls on the photo-cell. The slides ($B$, $D$ on the Plate) must be very free-running since movement of the axial arm of the arc ($H$, Fig. 1) is restrained only by the friction of the ball support. When light falls on the photo-cell the amplifier emits an intermittent current which causes a relay to oscillate with a low frequency. This in turn provides an intermittent current to a solenoid, at each oscillation of which a pawl engages with the teeth of a ratchet rack, moving the arm of the arc in such a way that the beam from the arc passes along the axis of the polarimeter.

The continuous operation of the arc is ensured by placing it in one arm of a Wheatstone bridge (Fig. 3). The armature coils of the motor ($M_1$), controlling its opening, are placed in the position normally occupied by the galvanometer. This mechanism works satisfactorily for periods up to 2 hr. without attention.

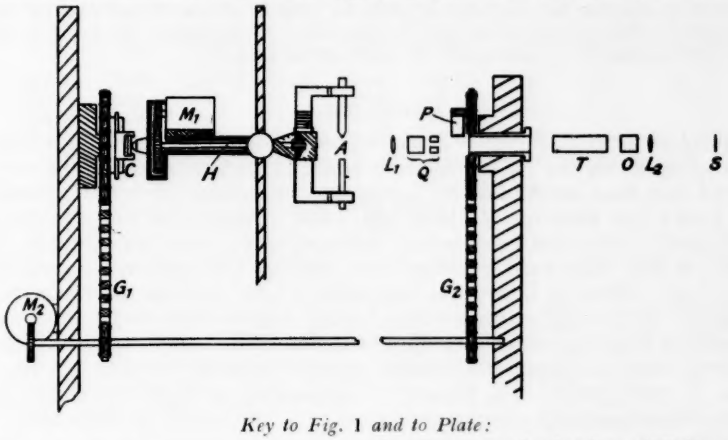



*Showing detail of the solenoid mechanism* (*C*, Fig. 1).

[*To face p.* 2954.

*Spectrograph.* A Hilger medium quartz spectrograph is used with Ilford Zenith Super Sensitive or Special Rapid plates. The position of the extinction on the plates is determined by means of a microphotometer in the region of high photographic density and low dispersion; below *ca.* 3000 Å visual inspection with a low-power microscope is better.

FIG. 1. *Elevation of the polarimeter and arc control (partly sectional—not to scale). The photo-cell rotates about the axis of the polarimeter. It is coupled by $G_1$ and $G_2$ to the solenoid mechanism so that an impulse from the cell is transmitted to the arc at the appropriate point in the revolution of the solenoid.*




*Key to Fig. 1 and to Plate:*

*A*, Arc.
*B*, Ratchet rack in slide.
*C*, Solenoid control mechanism.
*D*, Trolley running in cross slide, showing the ball which transmits the impetus of the solenoid to the axial arm of the arc (*H*, Fig. 1).
*E*, Pawl actuated by solenoid.
*F*, Solenoid.
$G_1$ & $G_2$, Chain drive.
*H*, Axial arm of arc.
$L_1$, Quartz condensing lens of 9″ focus.
$L_2$, Quartz–fluorite achromatic lens of 15″ focus.
$M_1$, Arc-control motor.
$M_2$, Driving motor for photo-cell and solenoid mechanism.
*O*, Analyser (Foucault prism).
*P*, Photo-cell.
*Q*, Polariser (Foucault prisms).
*S*, Slit of medium quartz spectrograph.
*T*, Polarimeter tube.

FIG. 2. *Circuit diagram of the photocell amplifier and oscillating relay: P*, Photo-cell; *U*, relay controlling the solenoid (*F*, on plate).

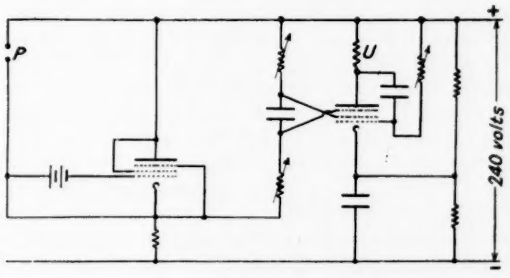
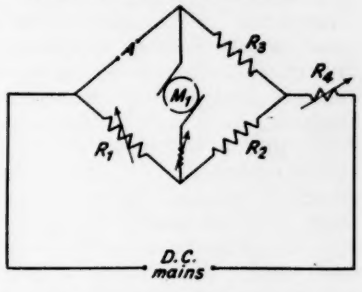



FIG. 3. *Arc-control circuit: A*, Arc. $M_1$, Armature coils of arc-control motor. $R_1$, $R_2$, $R_3$, and $R_4$, Resistances.




*Refractive Indices.*—A Pulfrich refractometer was used for these measurements.

*Densities.*—A 2-c.c. density bottle, with temperature control to within 0·1°, was used. Intermediate values were obtained by interpolation.

(+)-*Octan-2-ol.*—Prepared by Kenyon's method (*Org. Synth.*, 1926, **6**, 68), this had b. p. 85—86°/20 mm., $[\alpha]_D^{18}$ 11·76°.

n-*Heptane.*—Hydrocarbon supplied by the Anglo-American Oil Co. was dried ($P_2O_5$) and fractionally distilled, the fraction, b. p. 98·4°, being collected and stored over phosphoric oxide. It was redistilled immediately before use.

*Accuracy.*—Measurements made by finding the wave-length at which the three fields of the polarimeter appear of equal density on the plate have an accuracy of 0·3—1·0%. In view of the usual steep slope of the curve $\alpha/\lambda$ in the ultra-violet region the error in $\alpha$ may be several times larger. Where only the general shape of the curve is required, this method is satisfactory. For greater accuracy the method of "bracketting" (Lowry and Coode-Adams, *loc. cit.*) is employed, the limit of accuracy of which is often set by the absorption of light by the substance under investigation. For substances with strong absorption bands above 2000 Å the permissible path length is the chief factor governing accuracy and practicability of an investigation. A 2-dm. tube is suitable for aliphatic alcohols to 2500 Å, where an exposure of upwards of 2 hr. is required. For substances containing the phenyl chromophore, on the other hand, only a fraction of a centimetre is permissible for work below 4000 Å.

## Discussion

*Variations in Optical Rotatory Power.*—The validity of Drude's equation, $[\alpha]_\lambda = \Sigma k_x/(\lambda^2 - \lambda_x^2)$, relating the specific rotatory power $[\alpha]$ and the wave-length $\lambda$ at which it is measured, has been established by Lowry and his school (Lowry and Coode-Adams, *loc. cit.*; Lowry and Richards, *J.*, 1924, **125**, 1593). Subsequent theoretical expressions relating rotatory power and fundamental constants of the molecule (Condon, *Rev. Mod. Phys.*, 1937, **9**, 432; Kirkwood, *J. Chem. Phys.*, 1937, **5**, 479) embody a dispersion term of the Drude type. Whereas Lowry was interested to show that the dispersion curve could be represented by a very few Drude terms, Condon regards these terms as having average values resulting from the combination of several terms with more fundamental significance.

One of the interesting features of rotatory power is its marked dependence upon solvents (see Balfe, *J.*, 1950, 1871). The theoretical expressions obtained by Condon and others refer to an isolated molecule possessing freedom of rotation in all its single bonds. Such a state of affairs will generally exist only at relatively high temperatures in the dilute vapour phase, under which conditions optical rotatory power is not easily measured accurately. For this reason very few measurements of the rotatory power of vapours have been made, available data mainly referring to organic compounds in the liquid phase or in solution.

The aim of the present work is the study of the effect of conditions on the rotatory dispersion of simple organic substances. In this way, information as to the molecular state of the dissolved molecules can be obtained, and also, by eliminating the secondary factors, data can be provided for the estimation of the rotatory power of the free molecule for comparison with calculated values.

As a preliminary step, the optical rotatory disperion of (+)-octan-2-ol has been examined in the homogeneous state and in solution in *n*-heptane.

*Results.*—The early work on optical rotatory dispersion was concerned with the "simplicity" or "complexity" of the dispersion, *i.e.*, whether one or two terms of Drude's equation were required to represent the experimental curve. Condon (*loc. cit.*) has shown, theoretically, that the complexity of the dispersion has little fundamental significance. Whereas most previous authors had insisted that optical activity could only arise as a result of two or more oscillators coupled together, Condon, Altar, and Eyring (*J. Chem. Phys.*, 1937, **5**, 753) showed that a single electron moving in an asymmetric field could give rise to optical activity. In the light of this theory it is reasonable to suppose that all electronic transitions, in an active molecule, are optically active. This does not, however, imply that all absorption bands will show optical activity, since two transitions of approximately the same wave-length and intensity, and of opposite rotation, would cancel each other. The validity of the argument is rendered doubtful by the existence of substances exhibiting *simple* dispersion and yet containing well-spaced absorption bands: octan-2-ol is often quoted as a typical example. It is of interest, therefore (Tables 1 and 2), that the dispersions ratio $[\alpha]_{4358}/[\alpha]_{5461}$, which for the homogeneous material is 1·65, drops to 1·53 in a 10% *n*-heptane solution. If the *simple* dispersion law holds, then a dispersion ratio of 1·57 corresponds to an absorption band at zero wave-length, and a lower value to one of negative wave-length. Octan-2-ol must, therefore, be considered to show *complex* dispersion.

At higher temperatures the dispersion ratio of the pure substance rises slightly, and

on dilution with *n*-heptane it appears to have a minimum value at about 5% concentration. At the greater dilutions the value approaches that of the hot homogeneous substance. Small changes in the value of this quantity are not of much significance, being very sensitive to error. For this reason the values for the 1·25% solution are not given.

TABLE 1. *Specific rotatory power of* (+)-*octan-2-ol* (all wave-lengths in Å).

(*a*) Visible region.

| Temp. | $d_4^t$ * | λ 6438 | 5893 | 5780 | 5461 | 5086 | 4800 | 4678 | 4358 | $\frac{[\alpha]_{4358}}{[\alpha]_{5461}}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 24·6° | 0·8174 | 7·92° | 9·56° | 10·06° | 11·30° | 13·13° | 14·96° | 15·57° | 18·64° | 1·65 |
| 38·0 | 0·8066 | 7·18 | 9·20 | 9·76 | 10·98 | 12·75 | 14·66 | 15·02 | 17·87 | 1·64 |
| 56·0 | 0·7918 | 7·09 | 8·87 | 9·34 | 10·43 | 12·50 | 14·16 | 14·71 | 17·54 | 1·68 |
| 92·0 | 0·7615 | — | 8·77 | 9·30 | 10·40 | 12·37 | 14·02 | — | 17·40 | 1·68 |

* By interpolation from $d_4^{25\cdot0}$ 0·8174, $d_4^{50\cdot0}$ 0·7968, $d_4^{75\cdot0}$ 0·7766, $d_4^{100}$ 0·7547.

(*b*) Ultra-violet region.

| $t$ = 24·6°. | | | | $t$ = 38·0°. | | | | $t$ = 56·0°. | | $t$ = 92·0°. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $l$ = 2 dm. | | $l$ = 0·5 dm. | | $l$ = 2 dm. | | $l$ = 0·5 dm. | | $l$ = 0·5 dm. | | $l$ = 0·5 dm. | |
| λ | [α] | λ | [α] | λ | [α] | λ | [α] | λ | [α] | λ | [α] |
| 4260 | 20·31° | 3260 | 37·97° | 4460 | 17·14° | 3440 | 33·52° | 4130 | 20·91° | 4450 | 17·12° |
| 4050 | 23·31 | 3070 | 45·31 | 4150 | 20·57 | 3140 | 40·96 | 3950 | 22·79 | 3780 | 25·00 |
| 3810 | 26·29 | 2900 | 52·65 | 3930 | 23·59 | 2900 | 48·40 | 3850 | 24·05 | 3320 | 32·88 |
| 3640 | 29·29 | 2770 | 60·00 | 3760 | 26·64 | 2810 | 55·84 | 3450 | 31·62 | 3140 | 40·76 |
| 3490 | 32·28 | 2630 | 67·33 | 3600 | 29·67 | | | 3180 | 39·20 | | |
| 3330 | 35·26 | 2540 | 74·67 | 3500 | 30·86 | | | 2950 | 46·78 | | |
| | | 2490 | 82·02 | | | | | 2810 | 54·36 | | |

TABLE 2. *Specific rotatory power of solutions of* (+)-*octan-2-ol in* n-*heptane* (all wave-lengths in Å).

(*a*) Visible region.

| Temp. | $l$ (dm.) | $c$ (g./100 c.c.) | λ 6438 | 5893 | 5780 | 5461 | 5086 | 4800 | 4678 | 4358 | $\frac{[\alpha]_{4358}}{[\alpha]_{5461}}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 24·6° | 2 | 10·817 | 10·8° | 13·1° | 13·7° | 15·1° | 17·3° | 19·1° | 19·8° | 23·1° | 1·53 |
| 37·0 | 2 | 9·746 | 10·7 | 12·3 | 12·7 | 14·2 | 16·5 | — | — | 21·9 | 1·54 |
| 56·5 | 2 | 9·459 | 10·1 | 11·9 | 12·4 | 13·7 | 16·1 | — | — | 21·1 | 1·54 |
| 24·6 | 2 | 7·504 | 10·9 | 13·1 | 13·7 | 14·9 | 17·1 | 19·2 | 19·7 | 23·1 | 1·55 |
| 36·5 | 2 | 7·384 | 10·7 | 12·5 | 13·1 | 14·4 | 17·0 | 18·7 | 19·4 | 21·8 | 1·51 |
| 54·5 | 2 | 7·195 | 10·6 | 12·5 | 13·2 | 14·5 | 16·4 | 18·0 | 19·5 | 21·9 | 1·51 |
| 24·6 | 2 | 4·973 | 10·9 | 14·1 | 15·0 | 15·5 | 17·6 | 19·0 | 19·9 | 23·5 | 1·52 |
| 36·5 | 2 | 4·899 | 10·7 | 13·4 | 14·0 | 15·1 | 17·4 | 18·7 | 19·6 | 23·0 | 1·52 |
| 55·0 | 2 | 4·762 | 10·7 | 13·4 | 13·9 | 15·1 | 17·0 | 18·6 | 19·5 | 23·0 | 1·52 |
| 24·6 | 2 | 3·752 | — | — | 14·7 | 16·4 | — | — | — | 27·7 | 1·69 |
| 36·5 | 2 | 3·695 | — | — | 14·2 | 16·2 | — | — | — | 27·3 | 1·69 |
| 56·0 | 2 | 3·602 | — | — | 14·2 | 16·3 | — | — | — | 27·4 | 1·70 |
| 24·6 | 4 | 2·489 | — | — | 14·8 | 16·6 | — | — | — | 28·3 | 1·70 |
| 36·5 | 4 | 2·452 | — | — | 15·0 | 16·7 | — | — | — | 28·1 | 1·68 |
| 55·0 | 4 | 2·402 | — | — | 15·0 | 16·8 | — | — | — | 28·5 | 1·70 |
| 24·6 | 4 | 1·246 | — | — | 14·5 | 16·4 | — | — | — | 27·8 | — |
| 36·5 | 4 | 1·228 | — | — | 14·7 | 16·6 | — | — | — | 27·6 | — |
| 56·0 | 4 | 1·196 | — | — | 15·1 | 16·8 | — | — | — | 27·8 | — |

(*b*) Ultra-violet region.

| $t$ = 24·6°; $c$ = 10·817. | | | | $t$ = 56·5°; $c$ = 10·301. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $l$ = 2 dm. | | $l$ = 2 dm. | | $l$ = 2 dm. | | $l$ = 2 dm. | | $l$ = 0·5 dm. | | $l$ = 0·5 dm. | |
| λ | [α] | λ | [α] | λ | [α] | λ | [α] | λ | [α] | λ | [α] |
| 4270 | 24·6° | 3190 | 49·5° | 4900 | 17·4° | 3900 | 27·7° | 3680 | 32·0° | 2980 | 67·8° |
| 3750 | 32·8 | 3000 | 57·9 | 4150 | 23·7 | 3730 | 30·6 | 3570 | 34·0 | 2880 | 74·3 |
| 3410 | 41·1 | | | | | | | 3100 | 53·1 | | |

Although there may be numerous factors influencing the dispersion, it is clear that at least two different absorption wave-lengths are involved and that more than one molecular species is contributing to the resultant effect. In its more general aspect, this emphasises the danger of drawing conclusions from measurements of rotatory power made at only one wave-length, and measurements are required over as wide a range of wave-lengths as possible. In this case the range covered was from 6400 to below 3000 Å. No marked deviation from the simple hyperbolic form of the curve was observed, either in the homogeneous material or in the 10% *n*-heptane solution. The more dilute solutions were not examined in the ultra-violet region, since their low dispersion would make the estimation of the extinction position inaccurate. No attempt was made to achieve the accuracy of the earlier work of Lowry and Richards (*loc. cit.*) since this accuracy was obtained at the

TABLE 3. *Refractive indices of octan-2-ol and* n-*heptane at* 24·6°.

| | Wave-length (Å). | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6438 | 5893 | 5780 | 5461 | 5086 | 4800 | 4678 |
| Octan-2-ol ..... | 1·4227 | 1·4237 | 1·4245 | 1·4260 | 1·4283 | 1·4300 | 1·4309 |
| *n*-Heptane ..... | 1·3842 | 1·3802 | 1·3859 | 1·3872 | 1·3893 | 1·3909 | 1·3919 |

cost of a very restricted wave-length coverage. In this investigation the range of conditions under which the substance was examined was much wider, and the examination was carried to much shorter wave-lengths. The agreement with the earlier work is satisfactory. The dispersion constant $\lambda_x^2$, determined for the homogeneous material at 24·6°, was 0·0243, and the rotation constant $k$, 3·091. Lowry and Richards found 0·0244 and 3·176, respectively, but did not state the temperature at which their measurements were made.

The dispersion curves for the homogeneous alcohol, and for the solutions, at the higher temperatures run parallel to the corresponding curve at 25°, and are practically superimposable, being indistinguishable at the shorter wave-lengths. The accuracy of the measurements in the ultra-violet region is of the order of 0·3—1·0%, the error being in the determination of the wave-length rather than of the rotatory power, which is known to the accuracy of setting of the polarimeter.

The specific rotatory power of solutions of (+)-octan-2-ol in *n*-heptane increases progressively with dilution until a concentration of about 3% is reached, whereat it becomes constant within the limits of experimental error. The reduction in rotatory power accompanying a rise in temperature is greatest in the 10% solution. When the results are corrected for the expansion of the solutions, as are the figures in Table 2, it is seen that if rise of temperature has any effect on the rotatory power of the dilute solutions it is to increase it slightly. This increase is, however, of the order of the individual error of the observation and may well have no significance.

It has been suggested (Kauzman, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 339) that the quantity $\Omega = 3[\alpha]/(n^2 + 2)$, called the " rotivity," should show less variation with change of solvent and temperature than the specific rotatory power itself. For (+)-octan-2-ol the proportional variation in $\Omega$ with temperature is rather less than that of $[\alpha]$, but with change of solvent the rotivity shows no greater constancy than does the rotatory power. Hence, although use of $\Omega$ instead of $[\alpha]$ may be of value with hydrocarbons such as pinane (Rule and Chambers, *J.*, 1937, 145), it is of much less value in the case of octan-2-ol, where stronger intermolecular forces come into play.

In conclusion, it may be said that the existence of more than one optically active absorption band in octan-2-ol is proved, and that the one-electron theory is supported. There are still insufficient data to enable the molecular state of the solute molecules to be determined, but at least two molecular species would appear to contribute to the rotatory power. It seems probable that the values of the rotatory power of (+)-octan-2-ol shown in dilute solution in *n*-heptane approximate more closely to those of the individual molecule than do those of the substance itself.

The behaviour of octan-2-ol is clearly too complicated to permit its use as a yardstick

in the investigation of other substances. It is hoped to extend this work by investigating the effect of solvents and of temperature on the rotatory power of simpler substances.

The author thanks the Central Research Fund Committee of the University of London for a grant towards the construction of the polarimeter. Thanks are also offered to Professor R. G. W. Norrish, F.R.S., for the loan of a set of Foucault prisms, to Dr. V. I. Little for the design of the circuit given in Fig. 2, and to the laboratory staff of Bedford College for their help with the construction of the apparatus. The author also expresses his grateful appreciation of the help given by Mr. H. Yates and Mr. C. Godfrey, of Messrs. Hilger and Watts, in matters of construction and design.

BEDFORD COLLEGE, REGENT'S PARK, N.W.1. [*Received, February 24th,* 1953.]

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## 589. *Low-temperature Absorption and Phosphorescence Spectra of Some Iodo-compounds.*

By J. FERGUSON and T. IREDALE.

Iodine-substituted single-ring compounds sometimes show diffuseness in their spectra and only feeble phosphorescence (triplet–singlet emission), because of the importance of the $N \rightarrow Q$ absorption (Mulliken) characteristic of the alkyl iodides. Low-temperature absorption spectra and phosphorescence of a number of these iodo-compounds have been measured, and the significance of this phenomenon emphasised, except in the case of the iodobenzoic acids, where phosphorescence is relatively strong.

*Methyl Iodide.*—In the spectra of all alkyl halides, the longest wave-length electronic absorption is a continuum. Mulliken treated these continua theoretically (*J. Chem. Phys.*, 1940, **8**, 382) and interpreted them as similar to the $N$–$Q$ type spectra of the halogen halides. He found a discrepancy, however, between the theoretical and the observed intensity for methyl iodide. Although at the time the extent of the long wave-length region was not kown for certain, Porret and Goodeve's work (*Trans. Faraday Soc.*, 1937, **33**, 690) suggested to Mulliken that at least a small fraction of molecules dissociate to give a $^2P_{3/2}$ iodine atom.

We have examined methyl iodide in light petroleum solution and also the pure liquid with the aid of the Beckman spectrophotometer, the absorption curve obtained being shown in Fig. 1. Reproduced with it is the curve obtained by Porret and Goodeve (*loc. cit.*) for the vapour. Our curve corroborates Mulliken's conclusions that in methyl iodide the majority of the intensity lies in the $N$–$Q_0$ transition, the $N$–$^3Q_1$ appearing weakly (limit about 5000 Å), and it must be assumed that the weak $N$–$^1Q$ is well concealed under that of the $N$–$Q_0$.

Porret and Goodeve's work (*loc. cit.*) led them to believe in the existence of two maxima in the extinction curve, one at 38,800 and the other at 34,600 cm.$^{-1}$. After examination of the spectrum of methyl iodide in glassy solution at −180°, however, we find no evidence to support this supposition. We found only one maximum, corresponding to the one at 38,800 cm.$^{-1}$ in the vapour.

*Iodobenzene.*—It has been reported (Dunn and Iredale, *J.*, 1952, 1592) that the anomalous absorption intensity of iodobenzene in the 2600 Å region lies in a contribution from the $N$–$Q$ type transition present. The red shift of the $O,O$ band of iodobenzene in the vapour relative to that of benzene was given as about 1330 cm.$^{-1}$ as compared with 271, 1037, and 1093 cm.$^{-1}$ for fluoro-, chloro-, and bromo-benzene, respectively. A discussion of the "reversed" order of red shift and intensification is relevant. An explanation of this has been given by Matsen and Robertson (*J. Amer. Chem. Soc.*, 1950, **72**, 5252) but they had to resort to use of the inductive effect, the validity of which is open to question.

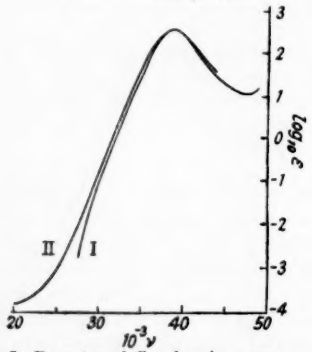
If we wish to discuss red shift and intensification along the lines suggested by Herzfeld (*Chem. Reviews*, 1947, **41**, 233) it is important to know the order of mesomeric electron

release in the ground state of the molecules under consideration. This order has been a matter of considerable dispute. The methods of determining it are of two types: (1) calculation of a mesomeric moment from dipole-moment measurements, and (2) the effect of nuclear attached halogen on the reactivities of aromatic side chains.

The first method involves treating the observed dipole moment as the vector sum of three moments, namely $m_{ind}$, the moment induced in the rest of the molecule by the polar carbon–halogen bond, $m_{prim}$, the moment of the carbon–halogen bond, and $m_e$ the moment due to the mesomeric migration of electrons into or out of the aromatic ring. The main causes of error in this method are (1) the difficulty of allowing for induction, *i.e.*, in evaluating $m_{ind}$, and (2) doubt as to how far it is correct to assume that the primary moments are equal in saturated and unsaturated compounds.

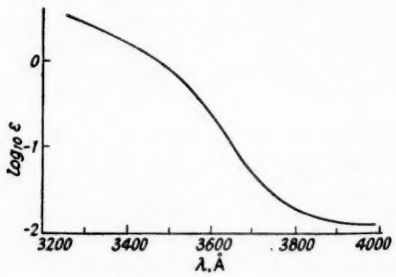
These intrinsic errors being disregarded, all the work published using this method (Sutton, *Proc. Roy. Soc.*, 1931, *A*, **133**, 668; Hugill, Coop, and Sutton, *Trans. Faraday Soc.*, 1938, **34**, 1534; Groves and Sugden, *J.*, 1937, 1992; Audsley and Goss, *J.*, 1942, 497), with the exception of that of Sutton who used solution measurements entirely, suffers from the lack of dipole-moment measurements on the vapours of the iodo-compounds involved.

FIG. 1. *Methyl iodide.*




I. Porret and Goodeve's curve.
II. Liquid and solution measurements.

FIG. 2. *Iodobenzene.*




These values have been obtained by the use of various solvent effect factors from solution measurements and prove completely inadequate.

However, the results of the second method are consistent and show that the mesomeric electron release decreases in the order F > Cl > Br > I. The evidence for this order was first obtained in 1926 (Shoesmith and Slater, *J.*, 1926, 216; Ingold, *Ann. Reports*, 1927, 156). The chemical evidence has been collated by Bennett and Baddeley (*J.*, 1933, 261; see also Bennett, *ibid.*, p. 1112) and recently it has been summarised and augmented by Baker and Hopkins (*J.*, 1949, 1089).

If, then, it is assumed that this order is the same in the excited state but that the decrease is much faster, we would expect the shift to be in the order found, *i.e.*, I > Br > Cl > F, if Herzfeld's ideas are valid. The justification for the much faster decrease for iodine over the other halogens for the excited state would come from the size of the *p* orbitals of iodine which would produce severe limitations upon mesomeric electron release.

The intensity of absorption will depend on the perturbation of both the ground and the excited states. It should be noted that mesomerism will tend to increase the charge distribution on the *ortho*-positions; this will then favour the transition under consideration, as the transition moment lies in the plane of the molecule perpendicular to the carbon–halogen bond. That the perturbation is relatively stronger for fluorine than for chlorine, etc., accounts for the high intensity of the spectrum of fluorobenzene and the fact that the allowed transition is many times stronger than the forbidden one, while for iodobenzene the intensity is low and the forbidden transition is much stronger than the allowed.

Although the appearance of the spectrum of iodobenzene would suggest that it has the least intensity of the halogenobenzenes, $\varepsilon_{max.}$ is 670 in solution. The reason for this has been discussed by Dunn and Iredale (*loc. cit.*).

We have also examined the spectrum of iodobenzene in solutions of high concentrations in order to determine the long wave-length limit as shown in Fig. 2. As can be seen, the limit is at about 4000 Å, thus showing that the $Q$ complex depends on the $N$–$Q_0$ transition for its intensity. It can then be said that the continuous spectra of methyl iodide and iodobenzene differ in that the transitions $N$–$^3Q_1$ and $N$–$Q_1$ play no part in determining the intensity of the absorption in iodobenzene, although their effect is quite noticeable in methyl iodide. The $Q_0$ state must then be responsible for the predissociation.

*Phosphorescence of Iodobenzene.*—Singlet–triplet absorption analogous to that in benzene should occur in the region 3500 Å. This transition can be seen in Fig. 2, though it is overlapped by the $N$–$Q$-type transition and appears only as a slight hump in this region. Attempts to obtain triplet–singlet phosphorescence emission from this level have not been very successful. H. J. Tinson in this laboratory has after much trial and error obtained a spectrum of the emission under rather drastic conditions. A faint spectrum was obtained after 7 hr.' exposure with a 0·8-mm. slit, a small Hilger spectrograph of very good light-gathering power being used. The spectrum was at first ascribed to the presence of an impurity; but after subsequent work on other iodo-compounds we are convinced of its validity. Although the high-energy end of the spectrum is very faint, it is the right spectral region, *i.e.*, about 3500—3600 Å.

From the work presented so far, we are able to gather that weak coupling takes place between the $Q_0$ state and the $B_1$ level of the $\pi$ system as a consequence of the close proximity and similar intensity of these two states. However, on further substitution, as shown below, the interaction between the two states is weakened mainly as a result of changes in position of the $\pi$ level with respect to that of the $Q_0$ state.

*Substituted Iodobenzenes.*—Until recently, little was known about the spectra of substituted iodobenzenes except the scanty information obtainable from solution measurements. Purvis (*J.*, 1911, **99**, 2318) attempted vapour measurements but reported continua for *o*- and *m*-iodotoluene and *o*- and *m*-di-iodobenzene. More recently Henri (*J. Phys. Radium*, 1928, **9**, 205) obtained continuous absorption for the three isomeric di-iodobenzenes in the vapour. Solution measurements have been very limited, Conrad–Billroth being the main contributor.

To gather further information, some new spectra have been investigated and some others repeated. The compounds were examined in light petroleum solution and some at −180° in a glassy solvent. The phosphorescence emissions of some of them have been examined and recorded. The simple *ortho*- and *meta*-monosubstituted iodobenzenes have the point group symmetry $C_s$. This is reflected most noticeably in their spectra. The *ortho*- and *meta*-derivatives have similar spectra, whilst those of the *para*-derivatives (point group $C_{2v}$) show higher intensities and greater red shift of the first two electronic transitions.

o-, m-, *and* p-*Chloroiodobenzene.*—These compounds were examined with the Beckman spectrophotometer in light petroleum solution. They had been examined by Conrad-Billroth and Förster (*Z. physikal. Chem.*, 1936, *B*, **33**, 311). The absorption curves are shown in Fig. 3. In order to examine the structure of the first electronic transition (the one similar to the $^1A_{1g} - {}^1B_{2u}$ transition in benzene) the absorption spectra of the three isomers were examined in light petroleum solution at −180°. The positions of the bands are shown in the Table, measurements being taken on the centre of each band. The positions of the four broad diffuse bands of the *para*-isomer are somewhat uncertain.

| *o*-Chloroiodobenzene | | | | *m*-Chloroiodobenzene | | | | *p*-Chloroiodobenzene | |
|---|---|---|---|---|---|---|---|---|---|
| Band | Å | Band | Å | Band | Å | Band | Å | Band | Å |
| 1 | 2805·5 | 6 | 2626 | 1 | 2817 | 6 | 2567 | 1 | 2855 |
| 2 | 2760·5 | 7 | 2587 | 2 | 2792 | 7 | 2569 | 2 | 2756 |
| 3 | 2733·5 | 8 | 2551 | 3 | 2710 | | | 3 | 2667 |
| 4 | 2699 | 9 | 2525 | 4 | 2667 | | | 4 | 2587 |
| 5 | 2657 | | | 5 | 2641 | | | | |

Because of the inherent diffuseness of these spectra it was not possible to carry out an accurate vibrational analysis.

The location of the *O,O* band in an electronic transition is facilitated by observing the spectrum at low temperature. As the temperature is lowered, thermal population of low vibrational states is very greatly decreased with subsequent intensification of transitions arising from the vibrationless ground state. By comparison of the spectrum at room with that at low temperature it is possible to determine which is the *O,O* transition, as the bands suffer only a very slight blue shift on lowering of temperature.

In accord with the symmetry of these compounds and the nature of the chlorine substituent, the first band observed in solution in each case proved to be the *O,O* transition.

The spectrum of the *ortho*-isomer when observed in the vapour has the same appearance as that at a low temperature with the exception that the bands are slightly less diffuse, this being most noticeable with the *O,O* transition. All the intense transitions in the vapour state therefore arise from the vibrationless ground state.

*Phosphorescence.*—The appearance of phosphorescence emission for these compounds was obtained by H. J. Tinson in this laboratory under rather drastic conditions (5 hr.' exposure with 0·5-mm. slit). The tracings from these plates are shown in Fig. 4. The

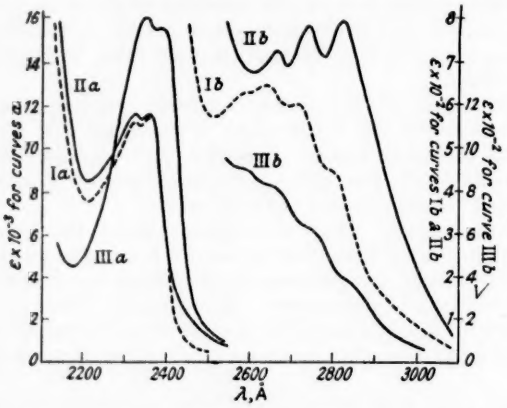



FIG. 3.
(I) o-, (II) m-, *and* (III) p-*Chloroiodobenzene.*

relative intensities of the emissions are not necessarily in the order shown. The emissions are stronger than that recorded for iodobenzene and are very diffuse. The energy order of the emissions is interesting, being in the direction $p > m > o$.

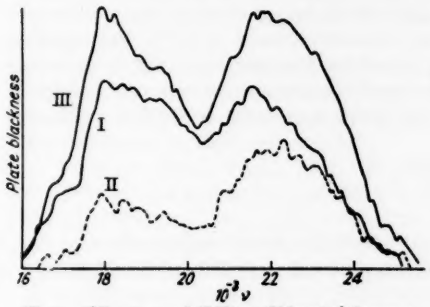
o-, m-, *and* p-*Iodonitrobenzene.*—The spectra of these compounds (Fig. 5), which have not been previously recorded, show the appearance of three electronic transitions in the region 2200—3000 Å and are easily identified with the corresponding transitions in nitrobenzene as given by Platt (*J. Chem. Phys.*, 1951, **19**, 101); for nitrobenzene, he gives two other transitions lying to shorter wave-lengths, one of which, in the region 2000 Å, is hinted at by the curve for the *ortho*-isomer which is beginning to turn at 2200 Å.

Evidence for the longest wave-length, low-intensity transition in nitrobenzene was first obtained by Hastings and Matsen (*J. Amer. Chem. Soc.*, 1948, **70**, 3514) and can be seen in solution measurements in light petroleum as a series of slight shoulders overlapped by the transition at 2700 Å. This transition is visible in both the *ortho*- and the *meta*-isomer, which show close relationship. It cannot be seen, however, for the *para*-isomer in the curve shown in Fig. 5, but is visible as a succession of shoulders when examined closely.

The second transition of benzene undergoes a large red shift in the order $o < m < p$, this transition being particularly susceptible to substitution, as pointed out by Doub and Vanderbelt (*J. Amer. Chem. Soc.*, 1947, **69**, 2714). The perturbation of the second singlet level then is in the order $o\text{-}C_6H_4I{\cdot}NO_2 < m\text{-}C_6H_4I{\cdot}NO_2 < Ph{\cdot}NO_2 < p\text{-}C_6H_4I{\cdot}NO_2$. The third transition shows the peculiarity experienced with all these compounds in that it shifts progressively to the blue as the second transition moves to the red. It shows also a remarkable decrease of intensity in the same sequence.

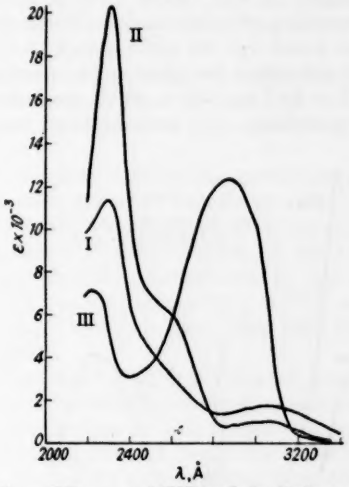
m- *and* p-*Bromoiodobenzene.*—The spectra of these two compounds in light petroleum are shown in Fig. 6. The same properties are observed as with the other compounds. In the *para*-isomer the second electronic transition has an extremely high extinction coefficient and has nearly completely overlapped the weak first electronic transition. The first electronic transition of the *meta*-isomer has a relatively well-defined vibrational structure, and the *O,O* transition (2825 Å) is of lower intensity than that of the corresponding chloro-compound, because of the reduced perturbation of the ring field by the bromine atom.

FIG. 4. *Phosphorescence emission.*



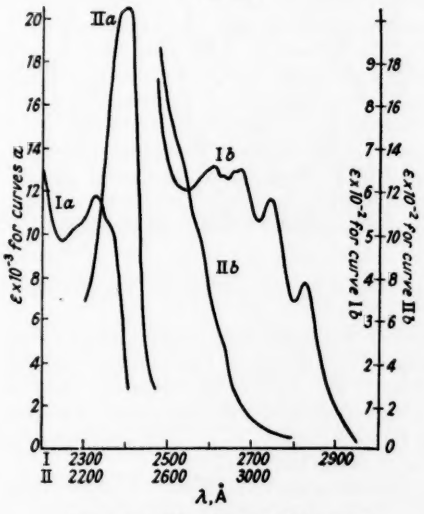

(I) o-, (II) m-, *and* (III) p-*Chloroiodobenzene.*

FIG. 5.




(I) o-, (II) m-, *and* (III) p-*Iodonitrobenzene.*

FIG. 6.




(I) m- *and* (II) p-*Bromoiodobenzene.*

FIG. 7. p-*Fluoroiodobenzene.*

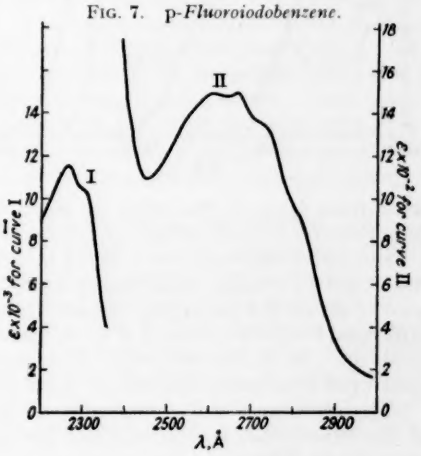



FIG. 7. p-*Fluoroiodobenzene.*

p-*Fluoroiodobenzene.*—The spectrum of this compound in light petroleum is shown in Fig. 7. It is different from that of the other *p*-halogenoiodobenzenes because of the reduced red shift brought about by the introduction of the fluorine atom in the nucleus. The second electronic transition has not overlapped the first transition which shows rather a high intensity. The spectrum has been reported by Conrad-Billroth and Förster (*loc. cit.*) but only in the region of the first electronic transition.

o-, m-, *and* p-*Iodobenzoic Acid.*—This series of compounds is perhaps the most interesting, as the parent compound, benzoic acid, has an easily measurable phosphorescence emission so that the effect of introducing an iodine atom should be easily determined. The spectra of the three isomers are shown in Fig. 8. All the features noted with the other series are present here.

*Phosphorescence.* The effect of the iodine atom on the phosphorescence emission proved noteworthy. The tracings are shown in Fig. 9. On using the same experimental conditions, it was found that the emission could only be photographed when the concentration of iodobenzoic acid was above a value which varied in the order $p < m \ll o$. It was found for the *ortho*-isomer that below the concentration $2 \times 10^{-4}$M the emission would not affect the plate. The corresponding values for the *meta*- and the *para*-isomer were $5 \times 10^{-5}$ and $3{\cdot}6 \times 10^{-5}$M, respectively. As the three isomers are not very soluble in light petroleum, the concentration range for the work was very restricted. All con-

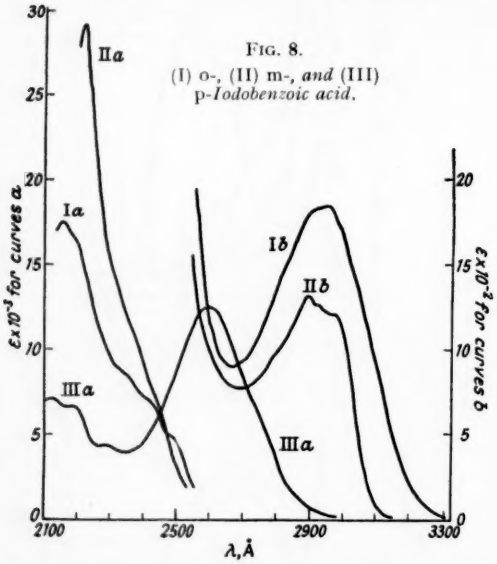



FIG. 8.
(I) o-, (II) m-, *and* (III) p-*Iodobenzoic acid.*

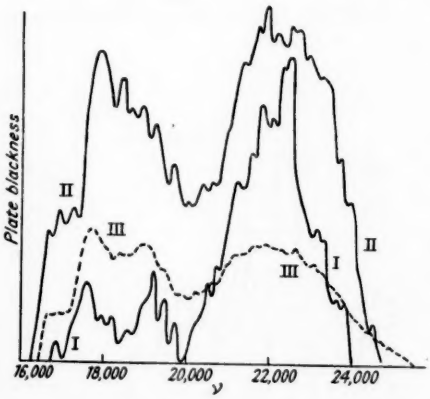



FIG. 9. *Phosphorescence emission.*
(I) o-, (II) m-, *and* (III) p-*Iodobenzoic acid.*

centrations refer to the value at room temperature, although under the experimental conditions contraction of the solvent takes place.

Successive exposures were taken in some cases on the same sample and the emission was found to weaken considerably upon irradiation. A red–purple Corex filter was also used to lessen the possibility of photodecomposition. The weakening of the emission on prolonged irradiation showed it to be due to the iodobenzoic acid and not to decomposition products. In all this work with iodo-compounds no formation of iodine takes place in the glass upon irradiation although it is instantaneous at room temperature.

The appearance and energy order of the three emissions are of interest. The spectrum of the *ortho*-isomer is relatively sharper than that of the *meta*, whilst that of the *para* is exceedingly diffuse.

The plates used are relatively insensitive in the green, which is responsible for the dip in all the tracing in this region, and cut off sharply at the red end so that all the tracings have similar long wave-length appearances.

*Discussion.*—From measurements in solution on substituted iodobenzenes we are able to observe the coarser features of the first three electronic transitions of these compounds. In every case the first electronic transition behaves as expected, *i.e.*, the order of red shift is from fluorine to iodine throughout a halogen sequence of one isomer, and for the three isomers of one compound the order of red shift is $o > m > p$. In halogen-substituted

benzenes, increase in atomic number of the substituent leads to great increase in intensity of the second transition and subsequent red shift. The absorption curves for *p*-fluoro- and *p*-bromo-iodobenzene show this effect admirably.

In a series of compounds, the position and intensity of the second transition in both the *ortho*- and the *meta*-isomer is very similar, whilst the *para*-compound exhibits larger intensification and red shift. In more complex compounds such as the iodonitrobenzenes and iodobenzoic acids, steric effects appear to affect the position and intensity of this transition in the *ortho*-isomer so that its energy lies above that of the parent compound. It is only in the *para*-compound that the transition lies at lower energies than in the parent compound.

The third transition could only be studied in the two series of more complex compounds (the iodonitrobenzenes and iodobenzoic acids) and exhibits peculiar characteristics. The energy order for the three isomers appears to lie in the direction $p > o > m$, whilst the intensity runs in the reverse order.

Platt (*J. Chem. Phys.*, 1951, **19**, 1418) has stated that opposed disubstitution inhibits *g*–*g* type transitions and intensifies *g*–*u* type. He cites this as an experimental test for the determination of the *g*–*g* or *g*–*u* nature of a transition. On applying these principles to the three transitions discussed above, we find that the first and second are of the *g*–*u* type whilst the third is *g*–*g*. As the second transition probably corresponds to the 2100 Å transition in benzene, this evidence would support the assignment $^1A_{1g} - {}^1B_{1u}$ and not $^1A_{1g} - {}^1E_{2g}$ as has recently been proposed by Craig (*Proc. Roy. Soc.*, 1950, **200**, 401) and Craig, Parr, and Ross (*J. Chem. Phys.*, 1950, **18**, 1561).

In absorption studies at $-180°$ attention was focused on the first electronic transition, as it has a sharp vibrational structure in benzene and irradiation in this region is responsible for the appearance of phosphorescence. The introduction of iodine into the ring predissociates this level and gives the vibrational structure a diffuse appearance. The amount of predissociation appears to be determined by the energy difference between the *N*–*Q* continuum and the quantised level. Thus iodobenzene shows a more diffuse vibrational structure than *o*-chloroiodobenzene because coupling with the *N*–*Q* continuum is much stronger in the former compound. Decrease in energy leakage in the singlet state then leads to a greater probability of phosphorescence emission from the triplet state.

That the effect of iodine is chiefly noted on the levels in the immediate vicinity of the $N$–$Q_0$ transition is shown by the iodonaphthalenes (unpublished work). Here the first singlet level is not in the vicinity of the peak of the $N$–$Q_0$ transition and is not perturbed to any measurable extent by it with the subsequent appearance of intense phosphorescence emission and stability. The second singlet, however, is perturbed fairly appreciably by the $N$–$Q_0$ transition in the region 2600—2700 Å.

The effect of iodine on the phosphorescence emission of benzoic acid has been given and as yet only the following conclusions can be drawn: (1) the rate of non-radiative internal conversion from singlet into triplet state is in the order $p > m \gg o$, or (2) the rate of radiative transition from ground triplet to ground singlet is in the order $o \gg m > p$. The rates in (2) being assumed to be of the same order, the first alternative would account for the experimental observation that under similar conditions the intensity of phosphorescence appears to be strongest for the *para*-isomer. As, however, the phosphoroscope was of a fixed-speed type, the apparent intensity could be due to much stronger coupling between ground triplet and singlet states for the *ortho*-isomer, resulting in shorter lifetime and apparent loss in intensity.

## Experimental

*Apparatus.*—Solution measurements were made with a Beckman DU Spectrophotometer. The apparatus used for the low-temperature work is of simple design, consisting of three units, the cell, cell holder, and outer container. The cell holder is filled with liquid oxygen or nitrogen, thus cooling the cell by conduction through a thin brass partition. The cell is of brass with silica end-pieces which are screwed into position. The light does not pass through the cooling agent, and condensation is prevented by evacuating the space between the cell holder and outer

container. The apparatus is then roughly a distorted Dewar flask with the cell inserted into a cavity in the inner wall.

A medium Hilger E III spectrograph was used for absorption measurements with the Beckman hydrogen lamp as a source of ultra-violet light.

The phosphoroscope has been described previously (Ferguson and Tinson, *J.*, 1952, 3083). The spectrograph used was a small Hilger E 420 F/4 instrument. A Baird Associates non-recording densitometer was used to examine the plates.

*Solvent.*—Light petroleum, b. p. 58—63°, was used as solvent in all the work, as it forms an excellent glass at low temperatures. Its purification has been described by Ferguson and Tinson (*loc. cit.*). The transparency of the glass thus formed to ultra-violet light is excellent.

*Purity of Compounds.*—All the compounds used were very carefully purified, the criterion of purity being constant spectroscopic properties. M. p. and b. p. data are not sufficient to specify the spectroscopic purity of a compound. It must possess constant absorption and emission properties. For the liquids, steam-distillation and subsequent vacuum-distillation at least twice were found sufficient to afford a pure liquid. The solids were recrystallised from an appropriate solvent and vacuum-sublimed at least three times.

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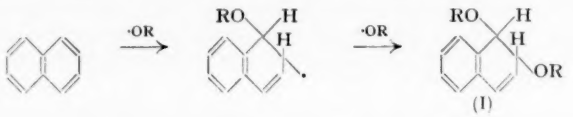
## 590. *The Action of Some Free Radicals on Naphthalene.*

By E. BOYLAND and PETER SIMS.

Naphthalene has been oxidised with Fenton's reagent, with aqueous hydrogen peroxide irradiated with ultra-violet light, and with benzoyl peroxide in chlorobenzene at 80°. 1-Naphthol and 2-naphthol or derivatives of them and salicylic acid have been obtained in all of these reactions. Oxidation with hydrogen peroxide in ultra-violet light has given isomeric hydroxybenzoic acids.

THE action of free hydroxyl and free benzoate radicals on naphthalene has been investigated for comparison with biological oxidation.

The metabolites isolated from the urine of animals dosed with naphthalene include 1-naphthol, both free and conjugated as sulphate and glucuronide (Lesnick, *Arch. exp. Path. Pharmak.*, 1888, **24**, 167), and *trans*-1 : 2-dihydronaphthalene-1 : 2-diol (I; R = H) (Young, *Biochem. J.*, 1947, **41**, 417; Booth and Boyland, *ibid.*, 1949, **44**, 361); recently, 2-naphthol also has been detected (Boyland and Solomon, unpublished observations). The action of such free radicals on naphthalene might be expected to produce 1- and 2-naphthols (free, or as their benzoates) by direct homolytic substitution on the one hand, and the diol (I; R = H or Bz), possibly formed by the mechanism suggested by Smith




(I)

(*Biochem. Soc. Symposia*, 1950, No. 5, 15), on the other. For a review of previous oxidations of naphthalene, see Schoental (*ibid.*, p. 3).

As sources of hydroxyl radicals, Fenton's reagent (cf. Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 333) and dilute aqueous hydrogen peroxide irradiated with ultra-violet light (cf. Weiss, *Discuss. Faraday Soc.*, 1952, **12**, 161) have been used. In both systems, the formation of hydroxyl radicals is well established, but other radicals, notably the $HO_2$ radical, may play some part in the reaction. Benzoate radicals were produced from

benzoyl peroxide in chlorobenzene at 80° by the method used by Roitt and Waters (*J.*, 1952, 2695).

The initial oxidations of naphthalene with Fenton's reagent were carried out in aqueous solution. Naphthalene is sparingly soluble in water, and only 5—10% of that dissolved was oxidised in any one reaction. The complex mixture of products was separated, after a preliminary division into acidic, phenolic, and neutral fractions, by paper chromatography. The nature of the acidic fraction, consisting of products derived from the ring-fission of naphthalene, is discussed below. Naphthalene was the only substance identified in the neutral fraction, careful search failing to reveal the presence of dinaphthyls. In the phenolic fraction 1- and 2-naphthol were identified, but two other phenols detected by paper chromatography could not be characterised although a number of possible intermediates in the oxidation were themselves treated with Fenton's reagent. Coumarin, obtained by Böeseken and von Königsfeldt (*Rec. Trav. chim.*, 1935, **54**, 313) by the action of peracetic acid on naphthalene, 1 : 1- and 2 : 2-dinaphthyl, and 1- and 2-naphthol all failed to give the unknown phenols under these conditions, whilst direct comparison on paper chromatograms showed that they were not dihydroxynaphthalenes or 1 : 1- or 2 : 2-dinaphthol. Both 1- and 2-naphthol were remarkably resistant to oxidation by Fenton's reagent and the only products obtained in each case were high-melting materials of unknown constitution, which are probably similar to the polymers obtained from the naphthols by peracetic acid oxidation (*idem*, *ibid.*) and by Elbs's persulphate oxidation (Desai and Sethna, *J. Indian Chem. Soc.*, 1951, **28**, 213). It has been suggested (Baker and Brown, *J.*, 1948, 2303) that the persulphate oxidation involves free sulphate-ion radicals, and Desai and Sethna (*loc. cit.*) obtained naphthalene-1 : 4-diol from 1-naphthol, and naphthalene-1 : 2-diol from 2-naphthol in this oxidation. No naphthalene diols were detected, however, among the products of the reaction of naphthols with Fenton's reagent.

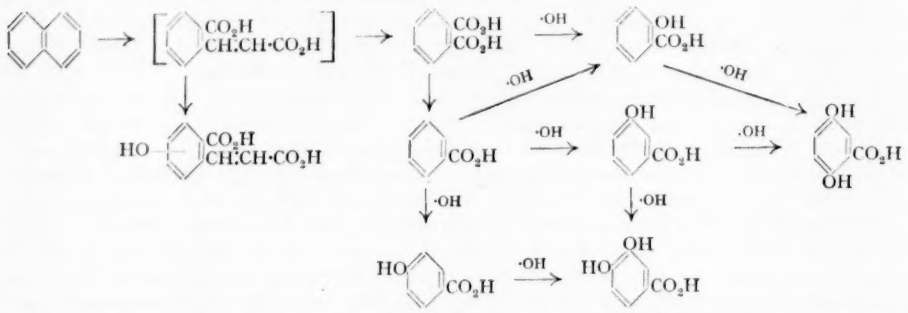
Weil-Malherbe (*Biochem. J.*, 1946, **40**, 351) has shown that the solubility of polycyclic hydrocarbons in aqueous purine solutions is higher than in water alone, and Booth and Boyland (personal communication) have found that this also applies to naphthalene. Experiment showed that with naphthalene the oxidation proceeds quite normally in the presence of caffeine (to give the products already described), in spite of the presence of a large excess of the purine. The caffeine was not attacked and was easily separated from the naphthalene oxidation products by suitable solvent extractions.

The products obtained from the oxidation of naphthalene with aqueous hydrogen peroxide, irradiated with ultra-violet light, depended largely on the concentration of hydrogen peroxide used. In about $2 \times 10^{-3}$M-hydrogen peroxide the products were mainly phenolic, but with $2 \times 10^{-2}$M-hydrogen peroxide, under the same experimental conditions, they consisted largely of hydroxybenzoic acids. At still higher peroxide concentration ($2 \times 10^{-1}$M) the products were again mainly acidic but irradiation was no longer necessary. Similar acidic products were obtained when 1- and 2-naphthol, 1 : 2- and 1 : 4-naphthaquinone, and *trans*-1 : 2-dihydronaphthalene-1 : 2-diol (I; R = H) were irradiated in the presence of 0·2M-hydrogen peroxide.

In the acidic fraction from the Fenton oxidation of naphthalene, salicylic acid was found, together with a phenolic acid apparently identical with one obtained from the oxidation of *o*-carboxycinnamic acid, which is presumably an *o*-carboxyhydroxycinnamic acid. Apart from the formation of this acid, *o*-carboxycinnamic acid is not appreciably attacked either by Fenton's reagent or by irradiated $2 \times 10^{-3}$M-hydrogen peroxide, whereas phthalic acid readily gives hydroxybenzoic acids under these conditions. Only with stronger hydrogen peroxide does *o*-carboxycinnamic acid give the hydroxybenzoic acids. With Fenton's reagent and with $2 \times 10^{-3}$M-hydrogen peroxide, irradiated with ultra-violet light, benzoic acid itself is converted into hydroxy-acids, whilst the monohydroxybenzoic acids are further hydroxylated. The nature of the products obtained from the irradiated hydrogen peroxide is independent of the pH of the solution. The products obtained in the above series of reactions are listed in Tables 4 and 5.

It seems probable, therefore, that the formation of the hydroxybenzoic acids from naphthalene takes place in two stages. The initial fission to give phthalic acid is a slow

reaction which is presumably brought about by some mechanism not involving the free hydroxyl radical, and is followed by the much more rapid reaction of phthalic acid with hydroxyl radicals to give the hydroxybenzoic acids :



Whether the formation of benzoic acid is an essential part of the mechanism, or whether there is, to a large extent, a direct replacement of carboxyl by hydroxyl groups is uncertain. The relative amounts of the monohydroxy-acids formed from phthalic acid differ from those found by Loebl, Stein, and Weiss (*J.*, 1951, 405) in the hydroxylation of benzoic acid with hydroxyl radicals produced by *X*-rays (see Table 2) and these authors report the formation in this reaction of diphenyl, which may have arisen from benzoic acid *via* the formation of free phenyl radicals.

The amounts of products formed have not been measured accurately, but, from the area of the spots on the chromatograms (Fisher, Parsons, and Holmes, *Nature*, 1949, **164**, 183; Boyland, Manson, Solomon, and Wiltshire, *Biochem. J.*, 1953, **53**, 420), estimates of the ratios of the amounts of 1- and 2-naphthol formed from naphthalene (Table 1), and of the amounts of hydroxy-acids formed from naphthalene, phthalic acid, and benzoic acid (Table 2), have been obtained.

TABLE 1. *Relative amounts of phenolic products from naphthalene.*

| Reaction | Ratio, 1-naphthol : 2-naphthol |
|---|---|
| Fenton's reagent | 3·8 : 1 |
| " " (in caffeine solution) | 3·5 : 1 (estimated from infra-red spectra) |
| $2 \times 10^{-3}$M-$H_2O_2$ (u.v. light) | 3·1 : 1 |
| Hydrolysis of (I; R = H) | 3·7 : 1 |

TABLE 2. *Relative amounts of phenolic acid products.*

| System | Benzoic acid : *o*-OH | *m*-OH | *p*-OH | 2 : 5-$(OH)_2$ | 3 : 4-$(OH)_2$ |
|---|---|---|---|---|---|
| Naphthalene in $2 \times 10^{-2}$M-$H_2O_2$ (u.v. light) ... | 10 | 5 | 2 | 1 | 1 |
| Phthalic acid in $2 \times 10^{-3}$M-$H_2O_2$ (u.v. light) ... | 10 | 5 | 1 | 3 | 1 |
| Benzoic acid in $2 \times 10^{-3}$M-$H_2O_2$ (u.v. light) ... | 10 | 5 | 5 | 2 | 8 |
| Aqueous benzoic acid (*X*-rays) * ... | 10 | 4 | 20 | — | — |

* Loebl *et al.*, *loc. cit.*

Treatment of naphthalene with benzoyl peroxide in chlorobenzene gave results which agree with those of Roitt *et al.* (*loc. cit.*) for the higher hydrocarbons, who found that the order of reactivity of these hydrocarbons followed the order of the " free valence numbers " of their reacting positions (Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553; Kooyman and Farenhorst, *Nature*, 1952, **169**, 153). Naphthalene, whose " free valence number " for the 1-position is close to that of phenanthrene and chrysene, behaves in a similar manner to these hydrocarbons and is not readily attacked by the benzoate radical. The reactivities of naphthalene, phenanthrene, and the very reactive anthracene are compared in Table 3. Dannley and Gippin (*J. Amer. Chem. Soc.*, 1952, **74**, 332) found that when 1-chloro-, -bromo-, and -nitro-naphthalene were treated with benzoyl peroxide, without use of an inert solvent, mainly 1 : 4- and 1 : 5-esters were obtained.

Roitt *et al.* (*loc. cit.*) were unable to isolate any phenanthrene reaction products and we have been unable to isolate any naphthyl benzoates. However, chromatographic separation of the reaction products on an alumina column enabled a mixture of the free

TABLE 3. *Reactions of some aromatic hydrocarbons.*

| Substance | $CO_2$, % † | $Ph{\cdot}CO_2H$, % ‡ | Hydrocarbon recovered, % |
|---|---|---|---|
| Anthracene * | 11·9 | 44·6 | 11·2 |
| Phenanthrene * | 48·9 | 28 | 85 |
| Naphthalene | 51 | 29 | 89 |

* Roitt *et al.* (*loc. cit.*).
† Calc. for $Ph{\cdot}CO{\cdot}O{\cdot}O{\cdot}COPh \longrightarrow 2Ph{\cdot}CO_2{\cdot}$; $Ph{\cdot}CO_2{\cdot} \longrightarrow Ph{\cdot} + CO_2$.
‡ Calc. for $Ph{\cdot}CO{\cdot}O{\cdot}O{\cdot}COPh \longrightarrow 2Ph{\cdot}CO_2{\cdot} + HX \longrightarrow Ph{\cdot}CO_2H$.

TABLE 4. *Products from oxidations with Fenton's reagent.*

| Substrate | Extent of oxidation as % of substrate | Products |
|---|---|---|
| Naphthalene | 5—10 | 1- and 2-Naphthol; salicylic and *o*-carboxyhydroxycinnamic acid; two unidentified phenols |
| Naphthalene + caffeine | 5—10 | As for naphthalene |
| *trans*-1 : 2-Dihydronaphthalene-1 : 2-diol (I; R = H) | — | 1- and 2-Naphthol |
| 1-Naphthol | 8 | Polymer |
| 2-Naphthol | 16 | Polymer |
| Phthalic acid | — | Monohydroxybenzoic acids; gentisic and protocatechuic acid |
| Benzoic acid | — | As for phthalic acid |
| Salicylic acid | — | Gentisic acid |
| *m*-Hydroxybenzoic acid | — | Gentisic and protocatechuic acid |
| *p*-Hydroxybenzoic acid | — | Protocatechuic acid |
| *o*-Carboxycinnamic acid | Trace | *o*-Carboxyhydroxycinnamic acid |
| Coumarin | — | Umbelliferone |
| 1 : 1′-Dinaphthyl | — | Nil |
| 2 : 2′-Dinaphthyl | — | Nil |

TABLE 5. *Products from oxidations with hydrogen peroxide irradiated with ultra-violet light.*[a]

| Substrate | $H_2O_2$ concn. (g.-mol./l.) | Products |
|---|---|---|
| Naphthalene | $2 \times 10^{-3}$ | 1- and 2-Naphthol; two unidentified phenols; trace of monohydroxybenzoic acids |
| Naphthalene | $2 \times 10^{-2}$ | Monohydroxybenzoic acids; gentisic and protocatechuic acid |
| Naphthalene | $2 \times 10^{-1}$ [b] | Hydroxybenzoic acids; benzoic and phthalic acid |
| 1-Naphthol | $2 \times 10^{-1}$ [b] | As for naphthalene |
| 2-Naphthol | $2 \times 10^{-1}$ [b] | As for naphthalene |
| *trans*-1 : 2-Dihydronaphthalene-1 : 2-diol (I; R = H) | $2 \times 10^{-1}$ [b] | As for naphthalene |
| 1 : 2-Naphthaquinone | $2 \times 10^{-1}$ [b] | As for naphthalene |
| 1 : 4-Naphthaquinone | $2 \times 10^{-1}$ [b] | As for naphthalene |
| Phthalic acid | $2 \times 10^{-3}$ [c] | Monohydroxybenzoic acids; gentisic and protocatechuic acid |
| Benzoic acid | $2 \times 10^{-3}$ [c] | As for phthalic acid |
| Salicylic acid | $2 \times 10^{-3}$ | Gentisic acid |
| *m*-Hydroxybenzoic acid | $2 \times 10^{-3}$ | Gentisic and protocatechuic acid |
| *p*-Hydroxybenzoic acid | $2 \times 10^{-3}$ | Protocatechuic acid |
| *o*-Carboxycinnamic acid | $2 \times 10^{-3}$ | Trace of *o*-carboxyhydroxycinnamic acid |
| *o*-Carboxycinnamic acid | $2 \times 10^{-2}$ | Monohydroxybenzoic acids |

[a] All reactions were carried out in solutions of pH 2, 6, and 10. [b] Duplicate oxidations carried out in the dark gave the same products. [c] Traces of these products were obtained when the reactions were carried out in the dark, or when an aqueous solution was irradiated with ultra-violet light.

naphthols to be obtained, whilst the presence of naphthyl benzoates in certain resinous fractions from the column seems probable, as both 1- and 2-naphthol were detected after their treatment with methanolic potassium hydroxide. Authentic 1- and 2-naphthyl

benzoate, when chromatographed under our experimental conditions, were partially hydrolysed to the free naphthols.

There is no evidence that dihydronaphthalene diols are formed in any of the above reactions. With Fenton's reagent, and with irradiated hydrogen peroxide, 1- and 2-naphthol are formed from synthetic *trans*-1 : 2-dihydronaphthalene-1 : 2-diol (I; R = H). Natural *trans*-1 : 2-dihydronaphthalene-1 : 2-diol affords 1-naphthol on treatment with mineral acid (Young, *loc. cit.*; Booth and Boyland, *loc. cit.*; see also Badger, *J.*, 1949, 2497), but experiments described below show that synthetic diol (I; R = H) is converted into both 1- and 2-naphthol (see Table 1). The diol benzoate (I; R = COPh) is hydrolysed to the free diol (I; R = H) by methanolic potassium hydroxide. The neutral fractions from oxidation by both Fenton's reagent and irradiated hydrogen peroxide, after treatment with mineral acid, did not give reactions for naphthols with diazotised *p*-nitroaniline, whilst the various resinous fractions from the benzoyl peroxide reaction after alkaline hydrolyses showed no increase in naphthol content on subsequent treatment with mineral acid. The hydroxylation of naphthalene by means of free-radical reactions resembles the biological mechanism in that 1- and 2-naphthol are formed, but it cannot account for the formation of *trans*-1 : 2-dihydronaphthalene-1 : 2-diol (I; R = H).

## Experimental

*Materials.*—Naphthalene was purified by washing an ethereal solution with aqueous sodium hydrogen carbonate and twice crystallising the recovered material from ethanol.

"AnalaR" hydrated ferrous sulphate and 30% hydrogen peroxide (supplied by Messrs. B.D.H. Ltd.) were used throughout.

*trans*-1 : 2-Dihydronaphthalene-1 : 2-diol (I; R = H) (Booth, Boyland, and Turner, *J.*, 1950, 1188) had m. p. 103°. Its *dibenzoate* (I; R = COPh) separated from ethanol as needles, m. p. 127—128° (Found: C, 77·7; H, 5·2. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%). When the benzoate (I; R = COPh) (250 mg.) was eluted from an alumina column with benzene (500 ml.), 250 mg. (92%), m. p. and mixed m. p. 127—128°, were recovered.

1- and 2-Naphthyl benzoate (250 mg.), similarly treated, were recovered (m. p. and mixed m. p.) in 44 and 50% yield, respectively. Subsequent elution of the columns with ether–methanol (500 c.c., 1 : 1) afforded 1-naphthol (22 mg., 15%), m. p. and mixed m. p. 93—94°, and 2-naphthol (31 mg., 21%), m. p. and mixed m. p. 120°, respectively.

*o*-Carboxycinnamic acid (Böeseken *et al.*, *loc. cit.*) separated from aqueous ethanol as needles, m. p. 201—202° (Found: C, 62·7; H, 4·3. Calc. for $C_{18}H_8O_4$: C, 62·5; H, 4·2%).

1 : 1′-Dinaphthyl (Smith, *J.*, 1879, 225) crystallised from light petroleum (b. p. 80—100°) in plates, m. p. 155°.

Naphthalene-1 : 2- and -1 : 4-diol (Desai *et al.*, *loc. cit.*) had m. p. 100—102° and 190°, respectively. The brown amorphous by-products obtained in these reactions were similar in appearance and properties to those obtained by the action of Fenton's reagent on the naphthols.

*Chromatography.*—Aluminium oxide (Savory and Moore) and Whatman No. 1 paper were used. The paper chromatograms were developed by means of three solvent systems: (A) 0·1N-aqueous ammonia (upward development); (B) *n*-butanol (4 vol.) and 0·1N-aqueous ammonia (1 vol.) (downward development); (C) *n*-butanol, pyridine, saturated aqueous sodium chloride, and ammonia (*d* 0·88) (4 : 8 : 5 : 3, by vol.) (downward development) (cf. Loebl *et al.*, *loc. cit.*).

The oxidation products were characterised on the paper (*a*) by examination under a Hanovia "Chromatolite" ultra-violet lamp, both before and after exposure to ammonia, (*b*) by spraying the paper with 0·3% aqueous diazotised *p*-nitroaniline and saturated aqueous sodium carbonate, and (*c*) by spraying the paper with saturated 2-chloro-4-nitrobenzenediazonium naphthalene-2-sulphonate (N.N.C.D. reagent; supplied by Messrs. Hopkin and Williams) in 0·1N-hydrochloric acid. Phenols detected by this last method were further characterised by noting the change in colour produced when the paper was subsequently sprayed with aqueous N-sodium hydroxide. In all cases, authentic specimens of the naphthols and hydroxybenzoic acids were run on the paper alongside the products obtained from the oxidation.

*Oxidation of Naphthalene with Fenton's Reagent.*—Saturated aqueous naphthalene (1 l.; *ca.* 30 mg. of naphthalene), containing ferrous sulphate (10 g.) and concentrated sulphuric acid (1 ml.), was stirred vigorously at room temperature, whilst aqueous 0·1M-hydrogen peroxide (100 ml.) was added in a thin stream. The solution was extracted with ether (3 × 100 ml.),

and the ethereal extract shaken with saturated aqueous sodium hydrogen carbonate (2 × 20 ml.). The acidic fraction was isolated as a brown gum (1·5 mg.) from the aqueous layer by acidification and extraction with ether (2 × 20 ml.), and was chromatographed on paper by development with solvents B and C (see Table 4). A phenolic acid present had the same properties as the phenolic acid obtained from the oxidation of *o*-carboxycinnamic acid (see below).

The phenolic fraction (4·5 mg.) was isolated from the first ethereal extract with 0·1N-sodium hydroxide, and was separated into its components on paper by development with solvents A and B (see Table 4). The two unknown phenols appeared, after exposure to ammonia, as violet fluorescent spots in ultra-violet light, and gave violet colours with diazotised *p*-nitroaniline and N.N.C.D. reagent.

The first ethereal extract was evaporated, the residue taken up in chloroform (10 ml.), and the solution washed with aqueous N-sodium hydroxide, dried ($Na_2SO_4$), and evaporated. The residue (21 mg.), after crystallisation from ethanol, formed plates, m. p. 80°, undepressed in admixture with naphthalene. The residue from the evaporation of the mother-liquors, after being heated on a water-bath for 15 min. with 2N-hydrochloric acid, gave no colour with diazotised *p*-nitroaniline.

*Oxidation of Naphthalene with Fenton's Reagent in the Presence of Caffeine.*—A saturated solution of naphthalene in saturated aqueous caffeine (1 l., *ca.* 300 mg. of naphthalene), prepared by shaking excess of the finely divided compounds with water at room temperature for several hours, and containing ferrous sulphate (50 g.) and concentrated sulphuric acid (5 ml.), was treated as before with aqueous 0·5M-hydrogen peroxide (100 ml.). The solution was extracted with ether (3 × 150 ml.), the ether evaporated, and the residue treated with aqueous N-sodium hydroxide (100 ml.). Extraction of the mixture with light petroleum (b. p. 40—60°) and evaporation of the solvent afforded naphthalene (120 mg.), m. p. and mixed m. p. 78—80°. The aqueous layer was washed with chloroform (6 × 20 ml.), acidified, and extracted with ether. Acidic (8·5 mg.) and phenolic (21 mg.) fractions were recovered from the ethereal extract as before and were separated into their components by paper chromatography (see Table 4). Evaporation of the ether left a small residue which gave no colour after acid hydrolysis and treatment with diazotised *p*-nitroaniline.

In a second experiment, naphthalene (1 g.) and excess of caffeine were heated in water (1 l.) to 60° for some hours. The mixture was filtered, and the filtrate quickly cooled to 30° by addition of crushed ice. Ferrous sulphate (200 g.) and concentrated sulphuric acid (10 ml.) were added, and the solution treated with aqueous M-hydrogen peroxide (200 ml.) as before. The phenolic fraction was isolated as a sticky solid (62 mg.) which was shown by infra-red analysis to contain 1-naphthol (73%) and 2-naphthol (23%).

*Oxidation of* 1- *and* 2-*Naphthol with Fenton's Reagent.*—1-Naphthol (250 mg.) in water (1 l.) containing ferrous sulphate (25 g.) and concentrated sulphuric acid (4 ml.) was treated with aqueous 0·1M-hydrogen peroxide (100 ml.) as before. The precipitate (15 mg.; m. p. >400°) which separated was soluble in aqueous sodium hydroxide and was reprecipitated as a brown powder on acidification. It was sparingly soluble in benzene, ethanol, and ethyl acetate, but it could not be obtained crystalline. On extraction of the filtrate with ether (3 × 250 ml.), 1-naphthol (230 mg., 92%), m. p. and mixed m. p. 94°, was recovered. No further products were identified when the mother-liquors from the crystallisation were examined on paper chromatograms developed with solvents A and B.

Similar treatment of 2-naphthol (250 mg.) afforded a brown powder, m. p. >400°, and 2-naphthol (210 mg., 84%), m. p. and mixed m. p. 122°, was recovered. No other products were identified.

*Oxidation of* o-*Carboxycinnamic Acid with Fenton's Reagent.*—*o*-Carboxycinnamic acid (20 mg.), suspended in water (1 l.) containing ferrous sulphate (10 g.) and concentrated sulphuric acid (1 ml.), was treated with aqueous 0·1M-hydrogen peroxide (100 ml.) as before. The products were isolated with ether as before, and chromatographed on paper by development with solvents B and C. A phenolic acid was detected, having the same $R_F$, giving the same violet fluorescence under the ultra-violet lamp, and forming the same red colours with diazotised *p*-nitroaniline and N.N.C.D. reagent as a phenolic acid found in the oxidation of naphthalene with Fenton's reagent.

*Other Oxidations with Fenton's Reagent.*—Samples (20 mg.) of the compounds listed in Table 4 and not described above were treated in ferrous sulphate (10 g.), concentrated sulphuric acid (1 ml.), and water (1 l.) with aqueous 0·1M-hydrogen peroxide (100 c.c.). The products, isolated as before, are listed in Table 4.

*Irradiation Experiments.*—Samples (5—10 mg.) of the compounds, dissolved or suspended in

aqueous hydrogen peroxide (200 ml.) of the required molarity and pH and contained in a quartz flask, were irradiated with light from a low-pressure high-tension ultra-violet lamp for 2 hr. The products, isolated as before, are listed in Table 5.

Benzoic acid was isolated from the acidic fractions of some of the above reaction mixtures, the fractions being kept for several days at room temperature. The needles which appeared were separated from the gum; in each case they had m. p. 118—120°, undepressed in admixtures with benzoic acid. Phthalic acid was detected in these gums by means of the fluorescence test.

*Hydrolysis of* trans-1 : 2-*Dihydronaphthalene*-1 : 2-*diol Benzoate.*—The benzoate (I; R = Bz) (250 mg.) was heated under reflux with 5% methanolic potassium hydroxide (5 ml.) for 30 min. *trans*-1 : 2-Dihydronaphthalene-1 : 2-diol (I; R = H) (81 mg., 77%), separating from benzene as needles, m. p. and mixed m. p. 101—102°, was isolated with ether. The evaporated mother-liquors gave no colour with diazotised *p*-nitroaniline.

The diol (I; R = H) (20 mg.) was hydrolysed by heating it with 2N-hydrochloric acid (5 ml.) on the water-bath for 15 min. Separation of the products on paper by development with solvent A showed the presence of both 1- and 2-naphthol (see Table 1).

*Action of Benzoyl Peroxide on Naphthalene.*—Naphthalene (12·8 g., 0·1 mole) and benzoyl peroxide (21·8 g., 0·1 mole) were heated at 80° in chlorobenzene (300 ml.) for 30 hr. (cf. Roitt *et al., loc. cit.*). Carbon dioxide (4·5 g., 51·2%) was evolved, and benzoic acid (7·25 g., 29·8%) was extracted from the cooled solution by means of aqueous sodium hydrogen carbonate. The solution was dried ($CaCl_2$), evaporated under reduced pressure, and kept at 0° overnight. Naphthalene (10·75 g.), m. p. and mixed m. p. 80°, was recovered by filtration. The filtrate was taken up in benzene–light petroleum (b. p. 60—80°) (50 ml.; 1 : 1) and chromatographed on an alumina column. Elution with light petroleum (b. p. 60—80°) afforded more naphthalene (0·65 g.), m. p. and mixed m. p. 80°.

Fractional elution of the column with benzene afforded a number of yellowish, non-crystallisable resins. Samples (10 mg.) of these fractions were treated with boiling N-methanolic potassium hydroxide (5 ml.) for 30 min., and aliquot portions (2 ml.) of the hydrolysate treated with diazotised *p*-nitroaniline (i) immediately and (ii) after 15 min.' heating on a water-bath with concentrated hydrochloric acid (1 ml.). The intensities of the azo-dye colours formed in each case were compared on a Gallenkamp colorimeter, an orange filter being used :

| Fraction | | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| Colorimeter readings | (i) | 82 | 78 | 62 | 71 | 25 | 17 |
| | (ii) | 80 | 79 | 58 | 68 | 30 | 15 |

Samples (20 mg.) of the above fractions were hydrolysed as before, and the products, in each case, isolated with ether. They were all shown, by means of paper chromatography used with solvent system A, to contain 1- and 2-naphthol, but no *trans*-1 : 2-dihydronaphthalene-1 : 2-diol (I; R = H) could be detected.

Elution of the column with ether–methanol (1 : 1) afforded a brown gum (240 mg.) which was shown on paper to contain 1- and 2-naphthol. An ethereal (20 ml.) solution of the gum was extracted with N-sodium hydroxide (3 × 20 ml.). 1-Naphthol (58 mg., 0·4%; m. p. and mixed m. p. 93—94° after crystallisation) separated from the acidified aqueous extract (Found : C, 83·1; H, 5·7. Calc. for $C_{10}H_8O$ : C, 83·3; H, 5·6%). The 3 : 5-dinitrobenzoate had m. p. and mixed m. p. 217—218°. 2-Naphthol was detected in the mother-liquors by means of paper chromatography.

We thank Mr. J. B. Solomon for advice on the paper chromatography, and Mr. S. F. D. Orr for the infra-red spectral analysis. The analyses were carried out in the microanalytical laboratory, Organic Chemistry Department, Imperial College of Science and Technology, by Mr. F. H. Oliver. The work has been supported by grants to the Royal Cancer Hospital and Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institutes of Health, U.S. Public Health Service.

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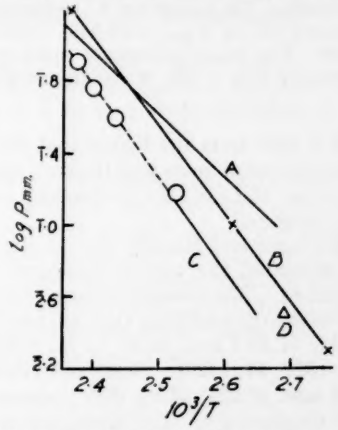
## 591. *Vapour Pressures and the Heats of Sublimation of Anthracene and of 9 : 10-Diphenylanthracene.*

By B. Stevens.

Vapour pressures and heats of sublimation of anthracene over the range 123—148°, and of 9 : 10-diphenylanthracene over the range 208—229° are determined by a fluorescence method. The values for anthracene are in good agreement with recent data, and when extrapolated to the melting point compare well with the value for the liquid at the same temperature obtained by previous workers.

During investigation of the fluorescence intensities, $F$, of anthracene and 9 : 10-diphenylanthracene as a function of concentration in the vapour phase, it was desirable to have reliable vapour-pressure data for these solids over the temperature ranges 120—217° (m. p.), and 200—248° (m. p.), respectively. No values seem to be available for the latter compound, whilst for anthracene the data of Niederschulte (Landolt–Börnstein, "Tabellen," Julius Springer, Berlin, 1912, 4th ed., p. 394), Mortimer and Murphy (*Ind. Eng. Chem.*, 1923, **15**, 1140), Mack (*J. Amer. Chem. Soc.*, 1925, **47**, 2473), Pringsheim ("Fluorescence and Phosphorescence," Interscience Publ., New York, 1949, p. 271), and Sears and Hopke (*J. Amer. Chem. Soc.*, 1949, **71**, 1732) are at variance or do not cover




*Vapour-pressure data of solid anthracene.*

*A*, Niederschulte. *B*, Pringsheim. *C*, Sears and Hopke. *D*, Mack. ○ denote values obtained by the fluorescence method.

the desired temperature range (see Figure). The method described below is not as accurate as the latest determination by Sears and Hopke (*loc. cit.*), but it is capable of extending the pressure range used by these workers and is insensitive to traces of volatile impurity.

### Experimental

*Method.*—A plot of log $F$ of anthracene vapour at constant temperature against the reciprocal of the temperature of solid ($1/T$) in equilibrium with the vapour is linear up to a solid temperature of *ca.* 150° in the apparatus used, and affords a value for the heat of sublimation ($L_s$). If the amount of solid used is such that it is completely vaporised at a temperature ($T_v$) below 150°, then the plot is linear up to $T_v$, above which log $F$ remains constant and a line of zero slope is obtained. The intercept of these lines gives $1/T_v$, at which temperature the vapour pressure may be calculated from the weight of solid taken and the temperature and volume of the cell. A similar plot for 9 : 10-diphenylanthracene is linear up to a solid temperature of *ca.* 230°, which, with 150° in the case of anthracene, imposes an upper limit on the temperature range over which the vapour pressures of these solids may be measured by this method with the degree of accuracy required.

*Materials.*—The anthracene was B.D.H. "Blue Fluorescence" quality, distilled twice from ethylene glycol and washed with hot water (Vogel, "Practical Organic Chemistry," Longmans Green, 1948, p. 826), and had m. p. 216·8—217·1°. 9 : 10-Diphenylanthracene was prepared according to Schlenk and Bergmann (*Annalen*, 1928, **463**, 148), and had m. p. 247—248°.

*Procedure.*—Pyrex tubes, *ca.* 7 cm. long and 1·4 cm. in internal diameter, containing small known quantities of anthracene in a lower limb *ca.* 5 cm. long and 0·6 cm. in internal diameter, were sealed in a vacuum and placed in a furnace at 200°. The lower limb rested in a hole in an aluminium block which could be electrically heated, thus controlling the temperature of solid anthracene; this temperature was recorded on a calibrated mercury thermometer resting in a second hole in the block. The vapour temperature was assumed to be that of the furnace which was controlled electrically to within 2°.

The small quantities of anthracene used were placed in the cells before evacuation in the form of benzene solutions of known strength and volume, and the solvent was evaporated by passage of a slow air current over the surface. This operation is responsible for the estimated experimental error of 5%.

The furnace was equipped with a window on to which the exciting radiation was directed by a half-silvered mirror, and from which the fluorescence intensities were measured. The light source, filters, and arrangement for measuring the fluorescence were otherwise as described by Metcalf and Bowen (*Proc. Roy. Soc.*, 1951, *A*, **206**, 437). The exciting radiation was cut off between readings to minimise any photo-reaction, and the observed fluorescence intensities were corrected for the light reflected from the surface of the cell.

Cell volumes were measured after the run by breaking off the tip and running in water from a standard burette.

Vapour pressures of 9 : 10-diphenylanthracene were measured in the same way, with a furnace temperature of 250°

*Results.*—The results for 9 : 10-diphenylanthracene obtained between 208° and 229° may be expressed as $\log P_{\text{mm.}} = 16{\cdot}058 - 8213/T$. The results for anthracene are plotted in the Figure. The mean percentage error in each case was 5%. The heats of sublimation are: anthracene 23·3 ± 0·5; 9 : 10-diphenylanthracene 37·5 ± 1·0 kcal./mole.

## Discussion

It is seen from the Figure that the vapour pressures obtained for anthracene lie on an extrapolation of Sears and Hopke's curve (*loc. cit.*), within the limits of experimental error. The value of $L_s$ is also in excellent agreement with that of 23·4 kcal./mole obtained by these workers.

Mortimer and Murphy (*loc. cit.*), and Nelson and Senseman (*Ind. Eng. Chem.*, 1922, **14**, 58), measured the vapour pressures of liquid anthracene, and their results are in good agreement. The former workers give an expression for the vapour-pressure curve of solid anthracene derived from their extrapolated liquid vapour pressure at the melting point and a value of 13·1 kcal./mole for $L_s$ obtained semi-empirically * (Mortimer, *J. Amer. Chem. Soc.*, 1922, **44**, 1429). Sears and Hopke (*loc. cit.*) use this expression to obtain a value of 0·353 mm. at 129° which they compare with their experimental value of 0·207 mm. at the same temperature. The divergence is not surprising in view of the fact that the $L_s$ values of the two workers differ to a similar extent.

A more valid comparison can be made between an extrapolation to the melting point from Sears and Hopke's value for the solid vapour pressure and Mortimer and Murphy's value for the liquid at the same temperature. If the melting point of anthracene is taken as 217°, these values are 3·87 and 3·95 mm. respectively, which are in good agreement.

In view of the confirmation at higher pressures by the present work, and the agreement on extrapolation with data for liquid anthracene, it seems that the expression $\log p_{\text{mm.}} = 12{\cdot}002 - 5102/T$ obtained by Sears and Hopke from their data in the range 105—125° may be used in calculating the vapour pressures of anthracene up to its melting point, without serious error.

This work was done under the supervision of Dr. E. J. Bowen, F.R.S., to whom the author is greatly indebted for advice and criticism. The author is grateful also to Mr. B. Brocklehurst for preparing the diphenylanthracene, and to the Department of Scientific and Industrial Research for a maintenance grant.

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South Parks Road, Oxford. [*Received, May 4th*, 1953.]

* This value of $L_s$ is calculated as the sum of the experimental heat of vaporisation of the liquid and the heat of fusion of the solid obtained empirically from $L_f = 12{\cdot}8 \times$ (m. p.).

# 592. *The Hydration and Hydrolysis of Anhydrous Aluminium Bromide.*

By Fred Fairbrother and William C. Frith.

A study has been made of the hydration and hydrolysis of anhydrous aluminium bromide, initially (*a*) in the vapour state, (*b*) as a crystalline solid, and (*c*) in solution in ether, with amounts of water ranging from traces up to that corresponding to $AlBr_3,6H_2O$.

The primary reaction appears to be a hydration which may or may not be followed by hydrolysis, depending upon the temperature of the reaction.

The results suggest a 3-stage hydration : (1) to a tetrahedrally co-ordinated $AlBr_3,H_2O$, followed by (2) the formation of an octahedrally co-ordinated $AlBr_3,3H_2O$ in which the aluminium–bromine bonds are still largely covalent, and (3) progressive displacement of the bromine atoms as negative ions by the co-ordination of additional molecules of water : $[AlBr_2,4H_2O]^+Br^-$; $[AlBr,5H_2O]^{2+}Br_2^{2-}$; $[Al,6H_2O]^{3+}Br_3^{3-}$, resulting finally in the formation of the hexahydrate, which is stable at room temperatures. Hydrolysis, which is very slow at room temperature, even with the most easily hydrolysable systems, and which becomes progressively slower and less in amount after 2—3 moles of water per mole of $Al_2Br_6$ have been added, is believed to be chiefly the result of the reaction of the still covalently bound bromine atoms with the adjacent water molecules.

The results indicate that the promoter effect of added aqueous hydrobromic acid on aluminium bromide or of aqueous hydrochloric acid on aluminium chloride, may be that of the water rather than that of the hydrogen halide.

It has long been known that addition of traces of water or of hydrogen halide to anhydrous aluminium chloride and aluminium bromide may materially improve their activities as catalysts in a number of reactions. Especially is this so in polymerisation and isomerisation reactions, in which indeed such an addition may be necessary in order to start the reaction. The rôle of the hydrogen halide has in the past usually been discussed in terms of the formation of a supposed hydrogen aluminium tetrahalide, $HAlCl_4$ or $HAlBr_4$, metallic salts of which are well known (cf. Leighton and Heldman, *J. Amer. Chem. Soc.*, 1943, **65**, 2276; Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," New York, 1941, Chapter 4).

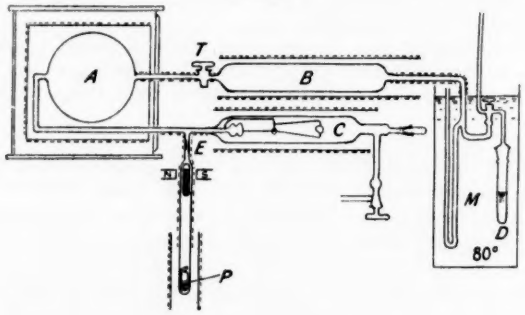
Recent work, however (Fontana and Herold, *J. Amer. Chem. Soc.*, 1948, **70**, 2881; Richardson and Benson, *ibid.*, 1951, **73**, 6096; Brown and Pearsall, *ibid.*, p. 4683), has shown that, at all events in binary systems of hydrogen halide and anhydrous aluminium halide, or in a ternary system involving also a saturated hydrocarbon such as *n*-butane, such halogeno-aluminium acids are in fact quite hypothetical and do not exist in any detectable amount even in circumstances which might be regarded as most favourable to their formation. It is only in the presence of a somewhat "basic" or electron-donor third component such as an olefinic or aromatic hydrocarbon that association of the hydrogen halide with the aluminium halide takes place. The action of added traces of water on these catalysts has also usually been interpreted as that of a hydrogen halide produced as the result of hydrolysis. Wackher and Pines, however (*ibid.*, 1946, **68**, 1642), have shown that not only does anhydrous hydrogen halide alone fail to promote the isomerisation of alkanes in the presence of aluminium chloride or bromide, but that the aluminium halides treated with various amounts of water and freed from uncombined hydrogen halide are quite effective catalysts, the most active being the one prepared by the action of 4 moles of water on one mole of aluminium bromide ($Al_2Br_6$). The same authors also showed that the amount of hydrogen bromide obtained by condensing water on to aluminium bromide at low temperatures and then heating to 100°, *decreased* as the proportion of water was increased, from 2·5 moles of HBr when 2 moles of water were added to one of $Al_2Br_6$, to zero when 12 moles of water were added.

We have now examined the reaction between anhydrous aluminium bromide and water in greater detail, with the aluminium bromide initially (*a*) in the vapour state, (*b*) as a crystalline solid, and (*c*) in solution in ether. The quantitative nature of the results varied over fairly wide limits as a consequence of the heterogeneity of most of the reactions involved; but the overall qualitative picture was always the same, namely, an initial hydration of the aluminium bromide, which may or may not be followed by hydrolysis and subsequent hydration of the products, according to the conditions of the reaction. At room temperature hydrolysis of a previously formed hydrate occurs only very slowly.

*Vapour-phase Hydrolysis.*—This aspect of the problem was of additional interest since it has been shown (Hudson, *Proc. I.U.P.A.C.*, 1947, **2**, 297) that a number of inorganic chlorides whose rapid hydrolysis in aqueous solution is a familiar phenomenon, *i.e.*, $PCl_3$, $SOCl_2$, $S_2Cl_2$, $SeOCl_2$, $SiCl_4$, do not in fact react easily with water vapour except as a heterogeneous reaction, whereas others such as $BF_3$ and $TiCl_4$ readily undergo a homogeneous reaction in the vapour phase.

A review of these limited results immediately suggests that it is only the "acceptor" or "Friedel–Crafts catalyst" type of halides which undergo vapour-phase hydrolysis and that they do so in the first place by co-ordination of a water molecule by the central atom. Accordingly, it was to be expected, and has been confirmed, that anhydrous aluminium bromide would readily undergo vapour phase hydrolysis.

FIG. 1.



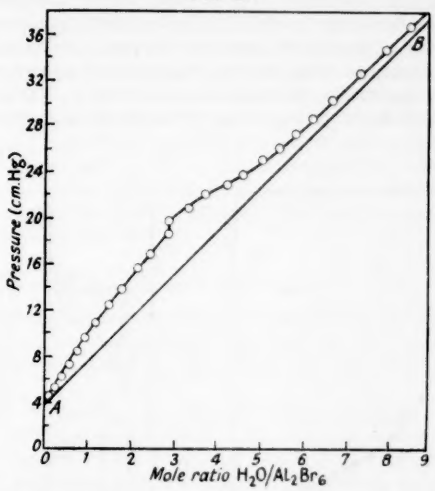

The apparatus used is shown in Fig. 1. The reaction vessel *A*, of about 1 l. capacity, the water-vapour reservoir *B*, of about 300 c.c., and the sensitive sickle gauge *C* were maintained at 160° ± 0·5° by three Cambridge thermocouple regulators. The sickle gauge was fitted with a mirror, operating on a torsional principle, which gave a 3-cm. deflection of a spot of light at 1 m. distance for a pressure difference of 1 mm. Hg; the deflection was linear with the pressure difference over a range of about ±15 mm. Hg. This gauge enabled instantaneous pressure readings to be made without the time lag associated with the adjustment of the external pressure in a simple sickle gauge. The gauge was brought to zero deflection before each addition of water vapour. The working temperature of 160° was chosen as being the lowest at which the vapour pressure of aluminium bromide (60 mm. Hg) was high enough to maintain sufficient halide in the reaction vessel in all experiments as an unsaturated vapour. A known amount of aluminium bromide, purified by at least six sublimations *in vacuo*, and sufficient to give an initial pressure in the reaction system of about 40 mm. Hg, was volatilised from the hook-ended ampoule *P* (Alexander and Fairbrother, *J.*, 1949, S223) into the reaction system, which was then sealed at *E*. Water vapour was admitted through the tap *T* (also maintained at 160°) in successive known small amounts which were calculated from the volume of *B* and its associated connecting tubes and the fall in pressure measured by the manometer *M*, which was kept at 80°. At the beginning of the experiment *B* was filled to a pressure of about 300 mm. Hg with water vapour from the reservoir of boiled distilled water *D*. The portion of the apparatus which gave the most trouble was the tap *T*. After many trials with a variety of devices, a well-fitting hollow-key Pyrex tap, wound with successive layers of copper foil, asbestos, and heating tape, and containing a thermometer bulb inside the connecting tube up against the key, was found to be the most suitable. The tap was greased with Dow Corning high-vacuum

grease and could be kept for about 3 days at 160° and turned 30—40 times before sticking or leaking.

Measurements of the total pressure in the reaction system were made by the sickle gauge immediately after each addition of water vapour and at intervals thereafter up to ½ hour, when a further addition of water vapour was made. In Figs. 2 and 3 are plotted, against the molar proportion of water added in one such "run," (*a*) (Fig. 2) the total pressure in the reaction system, and (*b*) (Fig. 3) the differential pressure $\Delta p$, *i.e.*, the *excess* pressure over that which would have been observed if no reaction had taken place. Each point shown corresponds to the pressure observed at the end of a half-hourly period.

Certain facts emerge from these results. At the temperature of the reaction aluminium

FIG. 2.




bromide is dimeric, so that we are dealing in the first place with the reaction of $Al_2Br_6$ molecules. If the net reaction had been of the form

$$Al_2Br_6 + H_2O = 2HBr + Al_2Br_4O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

no change in total pressure would have been observed, the oxybromide being assumed to be involatile (Line *AB*, Fig. 2; $\Delta p = 0$, Fig. 3). If the reaction had been

$$Al_2Br_6 + 2H_2O = 4HBr + 2AlBrO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

the reaction would have followed the line *AB* on Fig. 3 whilst if it had been

$$Al_2Br_6 + 3H_2O = 6HBr + Al_2O_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iii)$$

*i.e.*, a complete hydrolysis, the differential pressure would have been as at *AC*, Fig. 3. It will be observed that for the first few additions of water, up to something less than unity for the ratio $H_2O/Al_2Br_6$, whilst the aluminium bromide is still in large excess, the net reaction almost followed this course. The yield of hydrogen bromide, however, was never quite theoretical and soon fell below that of this simple hydrolysis reaction. Moreover, the reaction became gradually slower, so that in contrast to the early additions of water vapour, where the immediate increase of pressure was little less than that recorded after the lapse of ½ hour, even the half-hourly pressures recorded were no longer the limiting pressures. At *D*, where the differential pressure should have nearly double that observed if only the reaction (iii) had occurred, the half-hourly additions of water were interrupted and the system maintained at 160° for 10 hr., the pressure being noted at frequent intervals. Even after this lapse of time it was clear that the system had not reached equilibrium but was slowly approaching a less-than-theoretical yield asymptotically. A re-commencement of additions of water at *E* gave even less yields and eventually an apparent recession of the reaction set in. After a total of about 4 moles of $H_2O$ per mole of $Al_2Br_6$ had been added the pressures observed at the end of the half-hourly periods were actually *less* than those at the beginning.

The most probable explanation of this course of events would appear to be as follows.

Since, especially at the pressures used, we can exclude simultaneous collisions of an aluminium bromide molecule with two or three molecules of water, and in view of the well-known behaviour of aluminium bromide towards electron-donor molecules, the first stage must be the formation of a monohydrate: $Al_2Br_6 + H_2O = AlBr_3,H_2O + AlBr_3$, support for which is given by later experiments and which, whilst stable at low temperatures, rapidly decomposes even below 100° to give in turn $AlBr_2$·OH and AlBrO. The system is now heterogeneous and the $AlBr_2$·OH and AlBrO almost certainly undergo, at this stage, a rapid disproportionation into $Al_2Br_6$ and $Al_2O_3$ on the surface of the reaction vessel. This kind of disproportionation of an oxyhalide has been observed in other cases where the halide is volatile and in this instance is facilitated by the high lattice energy of the aluminium oxide. Thus, the final net reaction at this stage approaches the complete hydrolysis of Eqn. (i). It is to be noted that this only occurs in practice when the aluminium bromide is still in great excess and the products of hydrolysis are small in amount. As more water is added, however, hydrogen bromide accumulates in the vapour phase and the layer of hydrolysis products on the inner surface of the reaction vessel becomes thicker. Other reactions then become progressively more significant. Among these, which cannot be identified separately, the most important are probably: (*a*) the experimentally observed slowing down of the heterogeneous reaction of initial hydrolysis products, (*b*) the formation, by disproportionation, of thermally more stable hydrates, such as the hexahydrate, (*c*) a reversal, in the later stages of the reaction of the hydrolysis equation (iii) [we have also demonstrated the reversibility of this reaction by passing anhydrous hydrogen bromide over heated $\gamma$-$Al_2O_3,H_2O$ (Boehmite) which was prepared by dehydration of the precipitated hydroxide in a vacuum at 200°]; (*d*) an absorption of part of the added water vapour by the alumina. It may be noted that a similar effect to (*d*) was observed by Hudson (*loc. cit.*) in the case of titanium tetrachloride, at 25—100°, an initial rapid hydrolysis leading to the formation of the intermediate $Ti(OH)_2Cl_2$, followed by a subsequent slow absorption of water vapour on this solid particulate.

FIG. 3.

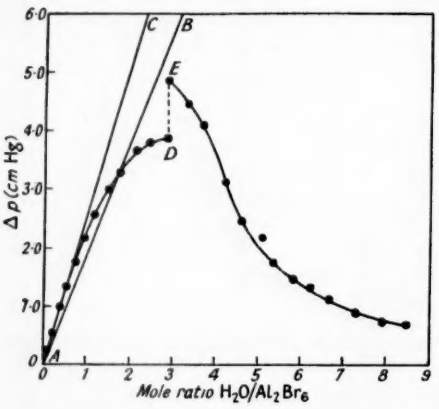
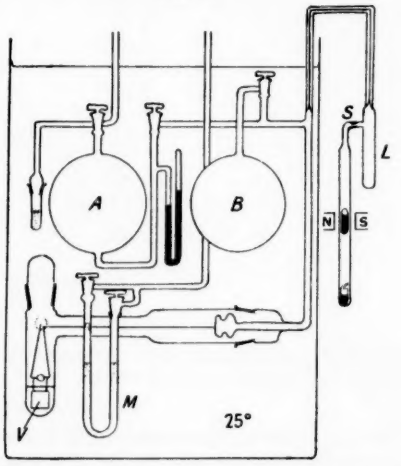



FIG. 4.




*Solid-phase Hydrolysis.*—These experiments consisted in the condensation of known amounts of water vapour on to crystalline aluminium bromide at −195°, followed by heating of the system to various temperatures up to 100° and the measurement of the pressure of the evolved hydrogen bromide.

The apparatus is illustrated in Fig. 4. Water vapour in known amounts, measured by the fall in pressure in the 1200-c.c. reservoir *A*, was condensed at −195° on to a known weight of pure aluminium bromide previously sublimed into the reaction vessel *L* which was sealed off at *S*. The reaction system, which included also a 1-l. bulb *B* (which could be used to increase the volume of the system when large amounts of hydrogen bromide were evolved), was otherwise evacuated and out-gassed. After the condensation of the required amount of water—which might require several fillings of the reservoir *A*—the reaction vessel *L* was surrounded by a constant-temperature bath at the desired temperature. In order to minimise dead space and

the effects of variation in room temperature, the connection between *L* and the rest of the apparatus, and which was outside the thermostats, was made of capillary tubing. Pressure measurements were made by means of an extremely sensitive sickle gauge, based on a design by Lewis and Style (*Nature*, **1937**, **139**, 631) and depending upon a bifilar suspension of the mirror for the amplification of small movements of the end of the sickle pointer. The movements of the mirror were damped by a vane *V* immersed in dibutyl phthalate. The pressure required to balance the gauge, which with its optical system was sensitive to $\pm 1{\cdot}5 \times 10^{-4}$ mm. Hg (for 1 mm. deflection at 1 m.) was measured by a mercury manometer, small pressure differences being measured directly by the gauge, which was calibrated for this purpose with the aid of the dibutyl phthalate manometer *M*.

A preliminary study in which, after condensation of the water on to the aluminium bromide at −195°, the vessel *L* was kept for 1 hr. at each of the following temperatures: −78° (acetone and solid carbon dioxide); −59° (melting chloroform); −44° (melting chlorobenzene); −33° (melting ethylene dichloride); −22° (melting carbon tetrachloride); −5·5° (ice and salt); 18° (room temperature), showed that hydrolysis began to take place, although extremely slowly, at temperatures as low as −40°: the amount, however, was sufficient to preclude the measurement of the dissociation of the hydrate, for which the sensitive gauge was designed.

As with the vapour-phase hydrolysis, small additions of water reacted relatively more completely and rapidly than larger ones. Even at room temperature, with sufficient water added to produce complete hydrolysis, less than 5% of hydrolysis (or 10% if the final product were hydroxy-halide) had occurred after 3 days. These points are illustrated below:

| | | | | | |
|---|---|---|---|---|---|
| $H_2O : Al_2Br_6$ | 0·46 | 1·11 | 1·14 | 2·28 | 3·01 |
| Reaction time (days) | 4 | 2 | 2 | 1 | 3 |
| Reaction % (on basis of 2 moles of HBr per mole of water added) | 8·6 | 2·4 | 6·6 | 1·6 | 4·5 |

The quantitative variability of the results serves to illustrate the heterogeneous nature of the reaction. It is doubtless to such a slow hydrolysis at room temperature that must be ascribed the internal pressure developed in old ampoules of commercial aluminium chloride or bromide.

In all cases, the pressure in the reaction system in the early stages was less than the vapour pressure of water at the particular temperature of *L*, although sufficient water was present to saturate the volume of the system. This confirms the idea of initial hydration. The absorption of a trace of water to give a hydrate with a negligible dissociation pressure, stable at ordinary temperature but dissociating on heating, has been described in the cases of niobium (columbium) and tantalum halides (Alexander and Fairbrother, *J.*, 1949, S223, 2472).

A series of experiments was carried out on systems similar to those studied by Wackher and Pines (*loc. cit.*) in which mixtures of aluminium bromide with known amounts of water, made at −195°, were kept for some time at about 20° and then heated to 100°, at which temperature they were maintained for several hours and until no further increase of pressure could be observed during 1 hr. The results are given in the annexed Table.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reaction time, hr. { at 20° | 48 | 14 | 18 | 40 | 6 | 18 | 60 |
| Reaction time, hr. { at 100° | 2 | 2 | 16 | 8 | 6 | 6 | 2 |
| Molar ratio, $H_2O : Al_2Br_6$ | 1·13 | 2·27 | 3·01 | 4·05 | 5·94 | 8·12 | 11·86 |
| Molar ratio, $HBr : Al_2Br_6$ | 2·25 | 3·21 | 3·11 | 2·38 | 2·11 | 1·83 | 0·63 |

Very little hydrogen bromide was evolved from these mixtures at room temperature. When the reaction vessel was warmed in a water-bath, the evolution, which was still slow up to about 70—75°, thereafter became more rapid, often with melting of the reaction mixture to a liquid which was very viscous even at 100° and solidified on cooling to room temperature.

It may again be observed that with small amounts of added water a nearly theoretical yield of two moles of hydrogen bromide per mole of added water is obtained. As more water is added the yield of hydrogen bromide per mole of $Al_2Br_6$ passes through a maximum and then decreases, so that when an amount of water almost sufficient to form the stable hexahydrate $AlBr_3,6H_2O$ is initially condensed on to the aluminium bromide, little more than one-tenth of the bromine is evolved as HBr on warming, an amount which might be expected to be obtained by heating the separately prepared hexahydrate at 100° for the same length of time.

*Hydrolysis in Ethereal Solution.*—Vapour-phase and solid-phase hydrolyses gave no experimental evidence of the formation of any intermediate hydrate, such as a trihydrate, which might reasonably be expected to be formed as a stage between a tetrahedrally co-ordinated monohydrate and the octahedrally co-ordinated hexahydrate. Evidence in this direction, however, was secured from experiments on the hydration of aluminium bromide in non-aqueous solution.

Since the dissolution of aluminium bromide in a large excess of water is exothermic to the extent of about 85 kcal. per mole of $AlBr_3$ (Berthelot, *Ann. Chim. Phys.*, 1878, **15**, 185), a calorimetric study of the hydration provides a convenient means of following the reaction. A similar approach has been used by Voigt (*Compt. rend.*, 1951, **232**, 26) to investigate the hydrolysis of phosphorus trichloride.

The study of the action of water on anhydrous aluminium bromide in non-aqueous solution, however, is additionally complicated by the fact that water is only sparingly soluble in all solvents in which aluminium bromide will dissolve as uncomplexed dimeric molecules. Consequently, even minute added droplets of water dissolve but slowly and there persists for some time a local excess of water at the periphery of the droplets so that the individual stages of hydration become smoothed out and hardly recognisable. Curves obtained for solutions in benzene and in chlorobenzene were of this nature but, though not sufficiently clear-cut in themselves, nevertheless offered supporting evidence to the results described below.

The most significant results were obtained by the study of the hydration in ethyl ether solution. Anhydrous aluminium bromide dissolves in ethyl ether as the monomer $AlBr_3$ (Wertyporoch, *Ber.*, 1931, **64**, 1370). One is therefore really dealing with the hydration of the ether complex, rather than with the unco-ordinated bromide, but the considerable heat developed

FIG. 5.

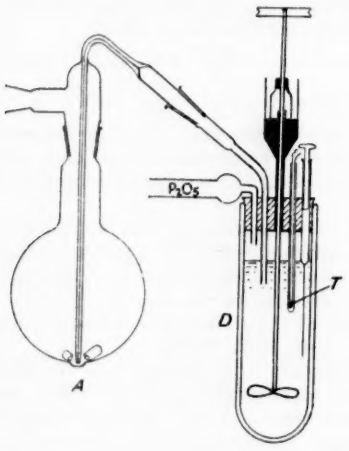
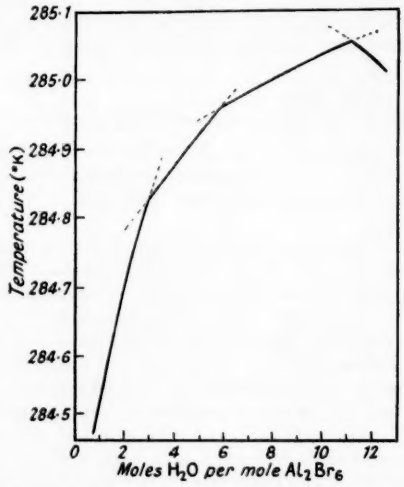



FIG. 6.




when water is added to a solution of aluminium bromide in excess of ether shows that water is much the more strongly held ligand, and the presence of ether is unlikely to affect the conclusions, regarding the stages of hydration, which may be drawn from the results.

It is in the nature of the reaction that after the first addition of water, however small, the system becomes heterogeneous. Nevertheless, by adding the water very slowly and with rapid stirring, the precipitate can be obtained in a very finely dispersed condition, permitting a much closer approach to homogeneity than is possible when the products are deposited on the sides of the reaction vessel. Under these conditions, evidence has been obtained of hydration, *without hydrolysis* to the hexahydrate through a trihydrate and a lower hydrate, probably the monohydrate.

The apparatus used for hydrolysis in ether is shown in Fig. 5. About 250 c.c. of pure dry ethyl ether were distilled into the flask *A*, and a weighed quantity of pure aluminium bromide, contained in a small ampoule, added. After dissolution of the halide, the whole of the liquid contents of *A*, with the exception of a few drops, were driven over by a stream of dry nitrogen into the unsilvered Dewar vessel *D*. This vessel was sealed against ingress of moisture and evaporation of the ether by a large rubber stopper carrying a stirrer, thermistor, and micrometer syringe. The liquid was stirred at a constant rate, and temperature changes were measured by means of the thermistor *T*. The latter was a Stanel type F.2311/300 element and was mounted inside a thin glass protective shield. The temperature–resistance relationship of the thermistor was determined over the range 10—30° by calibration against a standard mercury

thermometer: with the bridge arrangement employed, temperature changes of $\pm 0{\cdot}001°$ could be measured. There was observed a slight but steady upwards temperature drift due to the stirring, which however was small in comparison with the temperature rise due to hydration and was of no significance since we were only concerned with the relative temperature rises on the addition of equal amounts of water at the various stages of hydration. Water was added, as a liquid, by means of an all-glass micrometer syringe with an extremely fine tip which permitted the added water to be measured to 0·0002 c.c. Equal amounts of water (0·010 c.c.) were added at 5-min. intervals, and the temperature recorded after 2 and 4 min. and immediately before the next addition.

In Fig. 6 are shown the results of a typical experiment of this nature. The actual temperature rises in individual experiments varied with the concentration of the aluminium bromide used, but the breaks in the curves always occurred at the same place, namely, somewhat below 3 moles of $H_2O$ per mole of $Al_2Br_6$, sharply at 6 moles, and again at about 11—12 moles. The formation of mono-, tri-, and hexa-hydrate respectively would require 2, 6, and 12 moles of water. It might be expected therefore that a break in the curve should occur at 2 moles of water. Superficially the break at something below 3 moles of water recalls the maximum HBr evolution around the same proportion in the two previous cases. Consideration, however, shows that the situation is quite different in that evolution of HBr involves hydrolysis, whereas the experiments in ethereal solution involve only hydration since practically no hydrogen bromide can be detected in the filtered ethereal solution at the conclusion of the experiment. Nevertheless, it seems probable that this break at 3 moles has this in common with the two previous cases, that it is the result of the onset of a subsequent reaction before a previous one is complete.

A precipitate begins to form in the ethereal solution immediately on the addition of the first drop of water and increases throughout the first stage, by the end of which the reaction mixture has become quite opaque. If this precipitate were substantially a tri- or higher hydrate, or a product of hydrolysis caused by the reaction of the whole of the drop of water with the minimum of bromide in its immediate neighbourhood, the temperature–composition curve would be unbroken in its early stages. It must be remembered, however, that the water will be momentarily in excess before the drop dissolves, even with vigorous stirring, so the precipitate will not be a pure monohydrate, though this may be the main product of reaction at this stage, but will contain traces of a higher hydrate, probably the trihydrate. The formation of a 5-co-ordinated dihydrate $AlBr_3,2H_2O$ seems unlikely, and there is no experimental evidence for its existence. Hence the first break in the curve, which probably occurs when all the aluminium bromide has been precipitated from the ethereal solution, must occur at a molar ratio somewhat greater than 2 and its near coincidence with 3, corresponding to the formation of a $1\frac{1}{2}$ hydrate, seems to be fortuitous.

Beyond this stage, further reaction is heterogeneous, and the risk of temporary local excess concentrations of water much diminished. The anticipatory formation of a trihydrate therefore will not so much affect the location of the next break in the curve which always occurs sharply at 6 moles of water per mole of $Al_2Br_6$, corresponding to the formation of a trihydrate $AlBr_3,3H_2O$.

Near the conclusion of the hydration, as the formation of the hexahydrate nears completion, the reaction slows down and the system begins to cool as water is added, somewhat before the full 12 moles of water have been added.

The addition of water to more concentrated solutions of aluminium bromide in ether, *e.g.*, 20 g./l., produced temperature rises which could be measured with a mercury thermometer, but the results were less reproducible and some hydrolysis took place. When concentrations of 4—6 g./l. were used in the present experiments, no evolution of hydrogen bromide was observed and the filtered liquid at the end of the experiment gave negative tests for the presence of bromide, whilst analysis of the precipitate showed that it contained almost as great a proportion of bromine to aluminium as the original aluminium bromide.

## Discussion

In the light of the foregoing results, the mechanism of hydration, whereby the anhydrous crystalline mass of $Al_2Br_6$ molecules passes into the stable, ionic, and catalytically inactive hexahydrate $AlBr_3,6H_2O$, would appear to be as follows.

The first molecule of water to react with the bromide molecule brings about its dissociation and the formation of a tetrahedrally co-ordinated monohydrate $Br_3AlOH_2$. This is in accord with the general " acceptor " properties of aluminium bromide which, as the monomer $AlBr_3$, reacts with, and forms double compounds with, a variety of " donor "

molecules. Since the usual co-ordination number of aluminium is 6, the monohydrate can add further molecules of water up to a maximum of 3 without displacement of bromine, to form an octahedrally co-ordinated trihydrate, $AlBr_3,3H_2O$. These initial hydrates are stable at very low temperatures but decompose on heating, extremely slowly at room temperature, and fairly rapidly at 100°, to give a variety of hydrolysis products, which vary widely in composition according to the experimental conditions.

The corresponding slow hydrolysis of aluminium chloride has been known for a long time, it having been observed that " the reaction between moisture and aluminium chloride often does not take place at once but the hydrochloric acid is given off slowly on standing " (Ralston, Bureau of Mines Technical Paper, **321**, 1923; *Chem. News*, 1923, **127**, 246). This behaviour was ascribed to a slow diffusion of the hydrate water of a surface hexahydrate " glaze " into the interior of the mass, with the formation of aluminium oxide and hydrochloric acid. Why a trace of moisture should immediately form, without hydrolysis, a hexahydrate which subsequently dissociates and the water molecules of which diffuse into the interior and react with other aluminium chloride molecules, *with* hydrolysis, is not obvious.

A clearer picture, however, is obtained if we assume that at ordinary and medium temperatures, *i.e.*, below 100°, the hydrogen bromide evolved on hydrolysis is the result of reaction between the water molecules ($\not>3$ per $AlBr_3$) and the still mainly covalently bound bromine atoms attached to the same aluminium atom.

It has been shown by Palmer and Elliott (*J. Amer. Chem. Soc.*, 1938, **60**, 1852), by electron-diffraction measurements, that the lengths of the aluminium–bromine bonds in gaseous $Al_2Br_6$ molecules indicate that these already possess a considerable ionic character. Co-ordination of three water molecules to an $AlBr_3$ molecule would be expected still further to increase the ionic character of the Al–Br bonds and thus facilitate the displacement of a bromine atom as a negative ion on the approach of a fourth water molecule. Likewise, the addition of the fifth and the sixth water molecule finally results in a hexahydrated aluminium cation and three bromide ions. The hexahydrate is quite stable at ordinary temperatures, but decomposes on heating, slowly at 100° and more rapidly as the temperature is raised, with the simultaneous evolution of water and HBr. This hydrolysis on heating cannot be prevented by heating in HBr at atmospheric pressure.

The diminution in the amount of HBr evolved and the increasing slowness of the reaction as the amount of water is increased in the first two cases described above, can most easily be explained by the rearrangement in the solid phase of some of the water molecules to form a more stable hydrate with the accompanying ionisation of the bromine. The greater the number of water molecules present, the more likely would this be to occur before the hydrolysis of a lower hydrate was complete.

The above observations also suggest that in many cases, especially of isomerisation reactions or olefin alkylation, in which the addition of an aqueous solution of hydrogen halide has been observed to promote the reaction, the effect may not be that of the hydrogen halide but of the accompanying water. Aluminium chloride and bromide are excellent drying agents and will abstract water even from a hydrogen halide. In fact aluminium chloride was used by Burt and Gray (*Trans. Faraday Soc.*, 1911, **7**, 1) for this purpose in their determination of the atomic weight of chlorine from the density of hydrogen chloride.

Wackher and Pines (*loc. cit.*) suggested that the catalysts prepared by the action of water on aluminium halide probably consist of complexes which include aluminium halide, hydroxyaluminium halides, hydrogen halide, water, etc. It seems however, equally probable that the simple hydrates may be the effective catalysts in many reactions, by the formation of hydrogen-acids, *e.g.*, $[AlBr_3{\cdot}OH]^-H^+$, the proton then acting as a powerful positive ionogenic centre. This is similar to the action of water on boron trifluoride, the hydrates of which behave as $[BF_3{\cdot}OH]^-H^+$ or $[BF_3{\cdot}OH]^-OH_3^+$ (Greenwood and Martin, *J.*, 1951, 1795), and is also in accord with the well-known ability of various acids, *e.g.*, HF, $H_2SO_4$, $H_3PO_4$, to act as Friedel–Crafts catalysts, and with the behaviour of hydroxylic compounds as co-catalysts for the metal halide polymerisation of olefins.

THE UNIVERSITY, MANCHESTER, 13. [*Received, May 6th*, 1953.]

## 593. *Steroids. Part V.* Partial Synthesis of* 9 : 11-*Anhydrocorticosterone Acetate* [21-*Acetoxypregna*-4 : 9(11)-*diene*-3 : 20-*dione*].

By R. Casanova, C. W. Shoppee, and (in part) G. H. R. Summers.

Deoxycholic acid has been converted through *ætio*deoxycholic acid into methyl 3-oxoetia-4 : 9(11)-dienoate, which was also obtained from 9 : 11-anhydrocorticosterone by oxidation with periodic acid, and from corticosterone by oxidative degradation of the side-chain and dehydration of the resulting 11β-hydroxy-*ætio*-ester. By the diazo-ketone synthesis 3-oxoetia-4 : 9(11)-dienoic acid gave 21-acetoxypregna-4 : 9(11)-diene-3 : 20-dione (9 : 11-anhydrocorticosterone acetate),† which is one of the most active adreno-cortical hormones in respect of influence on mineral metabolism.

Corticosterone acetate (I) was found by Shoppee and Reichstein (*Helv. Chim. Acta*, 1943, **26**, 1316) to afford an anhydrocorticosterone † acetate, m. p. 159°, on gentle treatment with hydrochloric–acetic acid. This compound is now regarded as arising by an ionic 1 : 2-*trans*-elimination process (11β-OH/9α-H) and is formulated as (II*b*). Under more energetic conditions the anhydro-compound, m. p. 159°, was accompanied by a second anhydrocorticosterone acetate, m. p. 142°, which was shown to result from isomerisation of the former and was provisionally formulated as (III).

11 : 12-Anhydrocorticosterone acetate (III) was subsequently prepared by three different methods (ref. c ‡) and differs from both the above anhydro-compounds. It seemed therefore desirable to attempt to elucidate the structures of the compounds of m. p. 159° and 142°, and the present paper deals with the former of these, which is shown to be (II*b*). A future communication will deal with the anhydro-compound, m. p. 142°, which we regard provisionally as 8 : 9-dehydro-11-deoxycorticosterone acetate, although it has been formulated as 14 : 15-dehydro-11-deoxycorticosterone acetate by Fieser and Fieser (" Natural Compounds Related to Phenanthrene," Reinhold Publ. Corpn., New York, 3rd Edn., 1949, p. 409).

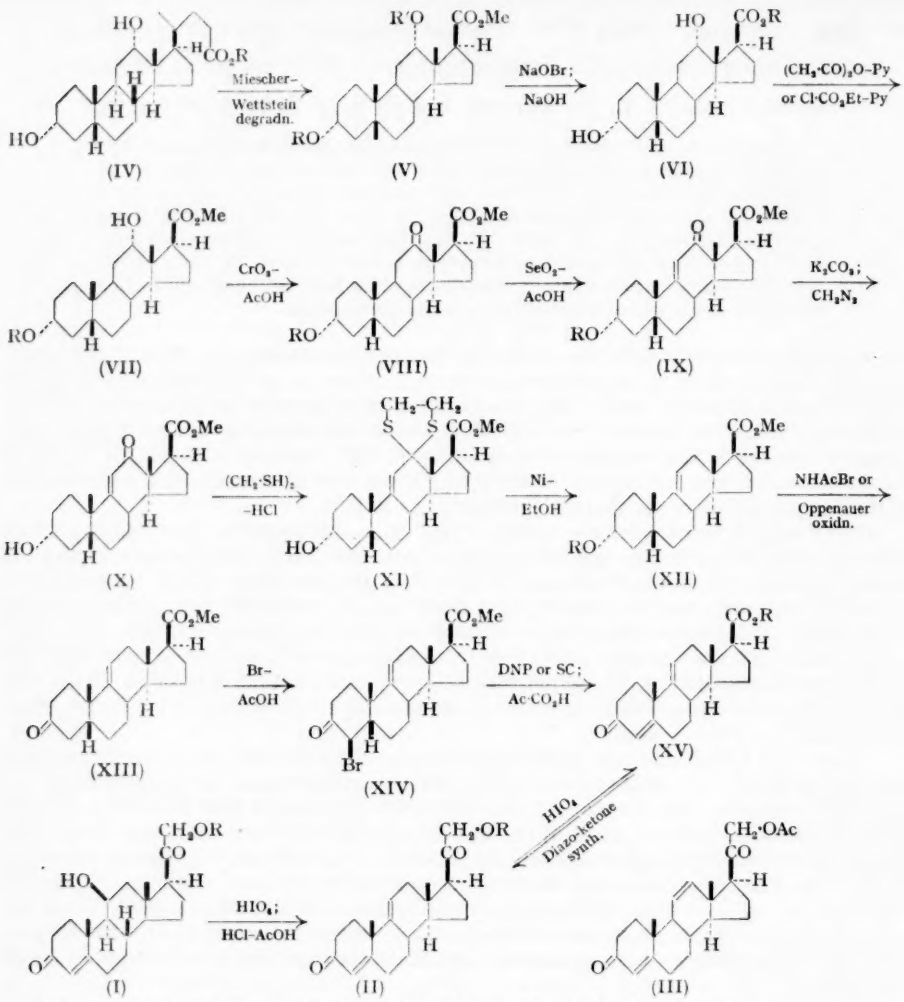
At the time (1949) that this work began, deoxycholic acid (IV*a*) was the only available starting material. Its methyl ester (IV*b*) with phenylmagnesium bromide gave 24 : 24-diphenylcholane-3α : 12α : 24-triol; acetic anhydride–pyridine at 100° converted this into a diacetate which, without purification, was dehydrated with hot acetic acid to 3α : 12α-diacetoxy-24 : 24-diphenylchol-23-ene. Application of the elegant degradation procedure of Meystre, Frey, Wettstein, and Miescher as modified by Meystre, Ehmann, Neher, and Miescher (ref. g) gave 12α-acetoxy-24 : 24-diphenylchola-20(22) : 23-dien-3α-ol, which was converted into the diacetate and oxidised with chromium trioxide at 15—20° to give, after partial hydrolysis with potassium carbonate, 12α-acetoxy-3α-hydroxypregnan-20-one (V*b*).

The further degradation of 3α : 12α-diacetoxypregnan-20-one (V*c*) has previously been carried out in five stages: conversion into the 21-benzylidene derivative, reacetylation, ozonolysis to the 20-keto-21-aldehyde, oxidation with periodic acid, and alkaline hydrolysis to give 36—44% yields of *ætio*deoxycholic acid (VI*a*) (refs. e, f). We have found that by oxidation with sodium hypobromite in aqueous dioxan at 0°, 3α : 12α-diacetoxypregnan-20-one gives in a single operation a 70% yield of pure *ætio*deoxycholic acid (VI*a*).

Methyl *ætio*deoxycholate (VI*b*), as its 3-(methyl succinate) (VII*a*), was oxidised with chromium trioxide to the 12-oxo-ester (VIII*a*) as described by M. Sorkin and Reichstein (ref. j; cf. Schwenk, Riegel, Moffett, and Stahl, *J. Amer. Chem. Soc.*, 1943, **65**, 549); this

* Part IV, *J.*, 1953, 1709. † Use of the prefix " anhydro " in this series to denote formation of an ethylenic bond by loss of H and OH from within one molecule is, of course, irregular. The systematic use of " anhydro " is to denote formation of an –O– bridge by loss of water between two OH in separate molecules (cf. acetic anhydride) or in one molecule (cf. anhydro-sugars). However, since the irregular use has been customary for some time in certain steroid papers and shows the relation of the products to corticosterone, these anhydro-names are used in the Introduction to this paper, but systematic names are used in the Experimental section.

‡ References given thus are to be found on p. 2985 annexed to the reaction scheme.




[Py = pyridine; DNP = 2 : 4-$(NO_2)_2C_6H_3$·NH·$NH_2$; SC = $NH_2$·CO·NH·$NH_2$].

| | M. p. | $[\alpha]_D$† | Ref.‡ |
|---|---|---|---|
| (I*a*) R = H | 180° | +223° E | a |
| (I*b*) R = Ac | 145 | +195 A | a, b |
| (II*a*) R = H | [not isolated] | | |
| (II*b*) R = Ac | 159 | +129 A | b, k |
| (III) | 180 | +178 A | c |
| (IV*a*) R = H | 176 | + 53 E | d |
| (IV*b*) R = Me | 81 | + 56 A | d |
| (V*a*) R = R′ = H | 167 | +165 A | e, f, g |
| (V*b*) R = H; R′ = Ac | 214 | +148 A | e, g |
| (V*c*) R = R′ = Ac | 118 | +190 A | e, f, g |
| (VI*a*) R = H | 298 | — | e, h |
| (VI*b*) R = Me | 115/145 | +105 M | h, i |
| (VII*a*) R = CO·$[CH_2]_2$·$CO_2$Me | 99 | — | j |
| (VII*b*) R = $CO_2$Et | Amorph. | — | k |
| (VIII*a*) R = CO·$[CH_2]_2$·$CO_2$Me | 152° | +115° C | k |
| (VIII*b*) R = $CO_2$Et | 125/156 | +138 C | k |
| (IX*a*) R = CO·$[CH_2]_2$·$CO_2$Me | 193 | +116 C | k |
| (IX*b*) R = $CO_2$Et | 161 | +103 C | k |
| (X) | 178 | +109 C | k |
| (XI) | 178 | — | k |
| (XII*a*) R = H | 131 | + 69 C | k |
| (XII*b*) R = Ac | 128/136 | + 88 A | l, m, n, o |
| (XIII) | 125 | + 56 C | k, l |
| (XIV) | 154 | + 84 C | k |
| (XV*a*) R = H | 240 * | — | k |
| (XV*b*) R = Me | 105 | +132 C | k |

* With decomp; † A = acetone; C = chloroform; D = dioxan; E = ethanol; M = methanol.

‡ See p. 2985.

by further oxidation with selenium dioxide in boiling acetic acid (Schwenk and Stahl, *Arch. Biochem.*, 1949, **14**, 125) gave the 3-(methyl succinate) of 3α-hydroxy-12-oxoeti-9(11)-enoate (IX*a*), with an absorption maximum at 239 mμ (log ε 4·14), hydrolysed by potassium carbonate to methyl 3α-hydroxy-12-oxoeti-9(11)-enoate (X) with an absorption maximum at 240 mμ (log ε 4·10). This sequence of reactions was also carried through with the 3α-hydroxyl group protected by condensation with ethyl chloroformate (cf. Borsche, *Ber.*, 1924, **57**, 1620; Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 5530; 1952, **74**, 3309); the 3α-ethoxycarbonyloxy-12α-hydroxy-ester (VII*b*) failed to crystallise but by oxidation with chromium trioxide gave the beautifully crystalline 3α-ethoxycarbonyloxy-12-oxo-ester (VIII*b*), converted by selenium dioxide–acetic acid into methyl 3*a*-ethoxycarbonyloxy-12-oxoeti-9(11)-enoate (IX*b*), showing maximum absorption at 239 mμ (log ε 4·07) and giving (X) by complete hydrolysis and re-esterification with diazomethane.

Reduction of the 12-oxo-ester (X) was unsuccessfully attempted by the Wolff–Kishner procedure, but was smoothly accomplished by conversion into the ethylene thioketal (XI) which by desulphurisation with W-7 Raney nickel gave methyl 3α-hydroxyeti-9(11)-enoate (XII*a*), characterised as the 3α-acetate (XII*b*). These compounds were first described by Lardon and Reichstein (ref. l); methyl 3α-acetoxy-11-oxoetianoate by energetic hydrogenation gave methyl 3α-acetoxy-11β-hydroxyetianoate, dehydrated by phosphorus oxychloride–pyridine at 18° to methyl 3α-acetoxyeti-9(11)-enoate (XII*b*), which by partial hydrolysis gave crude (XII*a*). The acetoxy-ester (XII*b*) has also been described, subsequently to our work, by Heymann and Fieser (ref. m), and, as an intermediate in their steroid total synthesis, by Woodward, Sondheimer, Taub, Heusler, and McLamore (refs. n, o). Acetylation of our 3α-hydroxy-ester (XII*a*) gave the 3α-acetate (XII*b*), double m. p. 127—128° and 135—136°, identical with specimens provided by Professor Reichstein and Professor Fieser.

Mild oxidation of 9 : 11-unsaturated steroids with chromium trioxide leads to 9 : 11-unsaturated 12-ketones and 9α : 11α-epoxides (Alther and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 492; Seebeck and Reichstein, *ibid.*, 1943, **26**, 536; Lardon and Reichstein, ref. l; Reich and Lardon, *ibid.*, 1947, **30**, 329; Shoppee, *ibid.*, 1947, **30**, 766). Formation of such by-products was avoided by oxidation with aluminium *iso*propoxide–*cyclo*hexanone or, better, *N*-bromoacetamide in aqueous *tert.*-butanol (cf. Kritchevsky and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 184) whereby the 3α-hydroxy-ester (XII*a*) gave methyl 3-oxoeti-9(11)-enoate (XIII). Bromination in acetic acid furnished the crystalline 4β-bromo-ester (XIV) in which the configuration of the bromine atom is assigned by analogy with the conclusions of R. N. Jones *et al.* (*ibid.*, 1952, **74**, 2828; cf. Djerassi, *J. Org. Chem.*, 1947, **12**, 823; *J. Amer. Chem. Soc.*, 1949, **71**, 1003), and of Fieser and Ettore (*ibid.*, 1953, **75**, 1700). The 4β-bromo-ester (XIV) was recovered unchanged after treatment with dry pyridine at 100—120° for 12 hours, but was smoothly dehydrobrominated by treatment with 2 : 4-dinitrophenylhydrazine (Mattox and Kendall, *ibid.*, 1948, **70**, 882; *J. Biol. Chem.*, 1950, **185**, 601; McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 3951) or, better,

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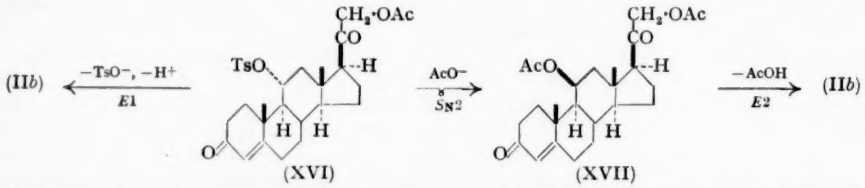
a, Reichstein, *Helv. Chim. Acta*, 1937, **20**, 953.
b, Shoppee and Reichstein, *ibid.*, 1943, **26**, 1316.
c, Meystre and Wettstein, *ibid.*, 1948, **31**, 1890; 1949, **32**, 880; von Euw and Reichstein, *ibid.*, 1948, **31**, 2076.
d, Reichstein and M. Sorkin, *ibid.*, 1942, **25**, 797.
e, Reichstein and von Arx, *ibid.*, 1940, **23**, 747.
f, Hoehn and Mason, *J. Amer. Chem. Soc.*, 1938, **60**, 1493, 2824; 1939, **61**, 1614.
g, Meystre, Frey, Wettstein, and Miescher, *Helv. Chim. Acta*, 1944, **27**, 1815; Meystre, Ehrmann, Neher, and Miescher, *ibid.*, 1945, **28**, 1252.
h, Mason and Hoehn, *J. Amer. Chem. Soc.*, 1938, **60**, 2824; 1939, **61**, 1614.
i, Wenner and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 965.
j, M. Sorkin and Reichstein, *ibid.*, 1946, **31**, 1218.
k, This paper.
l, Lardon and Reichstein, *Helv. Chim. Acta*, 1945, **30**, 1420.
m, Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 4054.
n, Woodward, Sondheimer, and Taub, *ibid.*, p. 4057.
o, Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4223.
p, Mason, Hoehn, McKenzie, and Kendall, *J. Biol. Chem.*, 1937, **120**, 719.
q, von Euw and Reichstein, *Helv. Chim. Acta*, 1947, **30**, 205.

with semicarbazide (Hershberg, *J. Org. Chem.*, 1948, **13**, 542; Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393) to give, after exchange with pyruvic acid–acetic acid buffered with sodium acetate (Sidgwick, "Organic Chemistry of Nitrogen," Oxford Univ. Press, 1942, p. 394; Conant and Bartlett, *J. Amer. Chem. Soc.*, 1932, **54**, 2881; Hershberg, *loc. cit.*), methyl 3-oxoetia-4 : 9(11)-dienoate (XV*b*), m. p. 104—105°, $[\alpha]_D$ +132°, $\lambda_{max.}$ 240 mμ (log ε 4·1).

3-Oxoetia-4 : 9(11)-dienoic acid (XV*a*) was obtained in the first instance in quantity insufficient to permit its conversion by the diazo-ketone synthesis into 9 : 11-anhydrocorticosterone acetate (II*b*). The latter was therefore hydrolysed with potassium hydrogen carbonate to 9 : 11-anhydrocorticosterone (II*a*) and this degraded by oxidation with periodic acid, to give after esterification with diazomethane methyl 3-oxoetia-4 : 9(11)-dienoate (XV*b*) identical with the synthetic product. Alternatively, corticosterone (I*a*) was oxidised with periodic acid to 11β-hydroxy-3-oxoeti-4-enoic acid (refs. p, q), dehydrated as the methyl ester by hot hydrochloric–acetic acid to give, after re-esterification, methyl 3-oxoetia-4 : 9(11)-dienoate (XV*b*). These reactions establish the structure of 9 : 11-anhydrocorticosterone acetate (II*b*).

{(Added in proof, June 15th, 1953). Since this paper was written, another preparation of 9 : 11-anhydrocorticosterone acetate has been described by Fried and Sabo (*J. Amer. Chem. Soc.*, 1953, **75**, 2273). 11-*epi*Corticosterone was successively converted into the 21-acetate and the 21-acetate 11α-toluene-*p*-sulphonate (XVI), which by treatment with sodium acetate in boiling acetic acid gave 9 : 11-anhydrocorticosterone acetate (II*b*), m. p. 160°, $[\alpha]_D$ +128°. Superficially the process appears to involve *cis*-9 : 11-elimination [9α-H(polar)/11α-TsO(equatorial)] of toluene-*p*-sulphonic acid; it seems more probable that the reaction proceeds either by heterolysis of the 11α-toluene-*p*-sulphonate group to give a carbonium ion which achieves neutrality by elimination of the tertiary 9α-hydrogen atom as a proton, or by acetolysis of the 11α-toluene-*p*-sulphonate group to give, with inversion of configuration, the unknown corticosterone 11β : 21-diacetate (XVII), which then undergoes synchronous ionic *trans*-9 : 11-elimination [9α-H(polar/11β-AcO(polar)] of acetic acid (cf. Reichstein and Shoppee, *Helv. Chim. Acta*, 1940, **23**, 729; Shoppee, *ibid.*, p. 740)}.




Subsequently the partial synthesis was completed by Dr. Summers. 3-Oxoetia-4 : 9(11)-dienoic acid (XV*a*) with oxalyl chloride (cf. Sheehan, *J. Amer. Chem. Soc.*, 1952, **74**, 360) gave the acid chloride (cf. Wilds and Shunk, *J. Amer. Chem. Soc.*, 1948, **70**, 2427), which with diazomethane yielded the diazo-ketone, converted by treatment with acetic acid into 9 : 11-anhydro-corticosterone acetate (II*b*), m. p. 159°, $[\alpha]_D$ +129°, $\lambda_{max.}$ 240 mμ (log ε 4·12) (for infra-red spectrum see Experimental section).

9 : 11-Anhydrocorticosterone acetate (II*b*) was found to exhibit in the Everse–de Fremery test 2—3 times the activity of 11-deoxycorticosterone acetate, and to show approximately equal activity in the life-maintenance test in adrenalectomised young rats. Similarly 11 : 12-anhydrocorticosterone acetate (III) showed slightly lower activity than 11-deoxycorticosterone acetate in the life-maintenance test in rats and approximately equal activity in adrenalectomised dogs (ref. c; Wettstein, personal communication). It seemed therefore of interest to examine 9 : 11-anhydrocorticosterone (II*a*) by the new microbioassay for mineralocorticoid activity (Tait, Simpson, and Grundy, *Lancet*, 1952, 122) which is based on the urinary $^{24}Na$ : $^{42}K$ ratio in adrenalectomised rats; Dr. Tait and Mrs. Simpson find that 9 : 11-anhydrocorticosterone (II*a*) and its acetate (II*b*) yield single spots by paper chromatography, running slightly more polar than 11-deoxycorticosterone and its acetate respectively, and that 1 and 2 μg. of (II*a*) per rat give the same response

as 1 and 2 μg. of 11-deoxycorticosterone respectively, whilst a balanced assay on three groups of 8 rats gave the following values for the $^{24}Na : {}^{42}K$ ratio :

| Quantity administered (μg.) | 1 | 2 | 4 |
|---|---|---|---|
| 11-Deoxycorticosterone | 3·16 | 2·92 | 2·36 |
| 9 : 11-Anhydrocorticosterone | 3·18 | 2·90 | 2·33 |

9 : 11-Anhydrocorticosterone is thus one of the most active of the adrenocortical hormones in respect of influence on mineral metabolism.

Finally, 9 : 11-anhydrocorticosterone (II*a*) may be an intermediate in the biochemical oxygenation of steroids at $C_{(11)}$ if the conversion, by perfusion through isolated adrenal glands, by treatment with adrenal homogenates, or by incubation with species of *Streptomyces*, of 11-deoxycorticosterone or its acetate into corticosterone (I*a*) * or of substance S acetate to substance M (cortisol) * (Pincus *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3261; *Arch. Biochem.*, 1950, **25**, 457; Sweat *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 4056; McGinty *et al.*, *Science*, 1950, **112**, 506; Kahnt and Wettstein, *Helv. Chim. Acta*, 1951, **34**, 1790; Haines *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 2381), or the transformation, by fermentation with *Aspergillus niger* or *Rhizopus nigricans*, of 11-deoxycorticosterone or its acetate into 11-*epi*corticosterone * or of substance S into 11-*epi*-substance M * (Peterson, Murray, *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1871; 1953, **75**, 408, 412; Fried *et al.*, *ibid.*, 1952, **74**, 3962; Wettstein *et al.*, *Experientia*, 1952, **8**, 422), takes place by enzymic dehydrogenation succeeded by a biochemical non-Markovnikov hydration process. This possibility is analogous to the transformation in the Krebs cycle of succinic acid ⟶ fumaric acid ⟶ malic acid, and is being investigated by Dr. R. I. Dorfman (Worcester Foundation, Shrewsbury, Mass.) using 9 : 11-anhydrocorticosterone acetate (II) supplied by us. Similar experiments have recently been performed by Miescher, Wettstein, and Kahnt (*Acta Physiol. Latino Amer.*, 1953, **1**, in the press), who treated the 9 : 11-"anhydro"-derivative of substance M acetate with adrenal homogenates and demonstrated the formation of substance M (cortisol).

## Experimental

For general directions see *J.*, 1953, 243, 540, 1709. $[\alpha]_D$ are in $CHCl_3$, ultra-violet absorption spectra were determined in EtOH on a Unicam SP.500, and infra-red spectra on a Perkin–Elmer double-beam instrument.

3α : 12α-*Diacetoxy*-24 : 24-*diphenylchol*-23-*ene*.—Methyl 3α : 12α-dihydroxycholanoate (IV*b*) (50 g.) (ref. d) by treatment with phenylmagnesium bromide (ref. f) gave 24 : 24-diphenylcholane-3α : 12α : 24-triol, m. p. 109° after recrystallisation from methanol; acetic anhydride–pyridine (3 hr. at 100°) and then refluxing acetic acid (Morsman, Steiger, and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1) afforded 3α : 12α-diacetoxy-24 : 24-diphenylchol-23-ene, m. p. 157—159° (56 g., 76%) after several recrystallisations from methanol. Another run furnished a 75% yield of product of m. p. 156—159°.

3α : 12α-*Diacetoxy*-24 : 24-*diphenylchola*-20(22) : 23-*diene*.—Much difficulty was experienced in obtaining this compound as described by Miescher and Wettstein (*loc. cit.*), but the following procedure † finally proved satisfactory. 3α : 12α-Diacetoxy-24 : 24-diphenylchol-23-ene (10 g.; m. p. 157—159°), dissolved in carbon tetrachloride (90 c.c.; purified and dried), was refluxed with *N*-bromosuccinimide (30 g.), with irradiation (3 × 100-w. bulbs) in sunlight and with vigorous mechanical stirring for 10 min. The yellow solution was cooled with ice and filtered, and the filtrate refluxed for 4 hr. with exclusion of moisture. After removal of carbon tetrachloride the residue was dissolved in acetone, from which 3α : 12α-diacetoxy-24 : 24-diphenylchola-20(22) : 23-diene slowly separated in needles, m. p. 138—141° (2·37—4·06 g. in 5 runs). Partial hydrolysis of the material from the acetone mother-liquors with hot aqueous-methanolic potassium carbonate precipitated the 12α-monoacetate, forming needles, m. p., 228—230°, on recrystallisation from benzene, and chromatography on aluminium oxide of the material from the alkaline mother-liquors gave, on elution with ether–benzene (1 : 4 and 1 : 1), further quantities of the 12α-monoacetate, reacetylated with acetic anhydride–pyridine at 100° to the 3α : 12α-diacetate. One run under apparently identical conditions gave no yellow colour and was a failure; another, with 45 g. of starting material, on the other hand, furnished

* No instance of 11α-hydroxylation occurring in any mammalian tissue has been reported.

† Adopted after discussion with Dr. A. Wettstein in Basle, for which we are most grateful.

the 3α : 12α-diacetate, m. p. 136° (27·7 g.), and the 12α-monoacetate, m. p. 220—230° (6·56 g.), which together correspond to a yield of 75%.

3α : 12α-*Diacetoxypregnan*-20-*one* (V*a*).—Miescher and Wettstein's procedure (*loc. cit.*, p. 1823) was slightly modified by working at 5—10° for 4 hr. with mechanical stirring, and keeping the solution for 16 hr. at 15—20°. 3α : 12α-Diacetoxy-24 : 24-diphenylchola-20(22) : 23-diene (m. p. 138—142°; 35·6 g.) thus gave an oxidation product (32·3—32·5 g.), separated by use of Girard's reagent T into non-ketonic material (7·7—7·0 g.) and crude partly crystalline 3α : 12α-diacetoxypregnan-20-one (V*c*) (23·2—23·5 g.). The latter with aqueous methanolic potassium carbonate for 16 hr. at 20° gave 12α-acetoxy-3α-hydroxypregnan-20-one (V*b*), m. p. 203—207° (6·9—8·5 g.) after recrystallisation from methanol; the material from the mother-liquors (11·5—12·5 g.), by chromatography on aluminium oxide (300 g.) and elution with ether–benzene (1 : 4; 5 × 600 c.c.), gave a further quantity of crude crystalline 12α-monoacetate (V*b*) (3·5—3·3 g.) (total yield, 47—50%). For purification it was found advantageous to hydrolyse the 12α-monoacetate (15·4 g.) with 5% aqueous-methanolic potassium hydroxide for 2 hr.; saturation with carbon dioxide, vacuum-evaporation, extraction with ether, washing, drying, concentration, and addition of pentane yielded pure 3α : 12α-dihydroxypregnan-20-one (V*a*), m. p. 169—170° (9·6 g.) and m. p. 165—167° (1·4 g.) (83% isolation). Similarly the crude crystalline 12α-monoacetate (6·8 g.) by hydrolysis gave the diol (V*a*), m. p. 168—169° (3·7 g.) and m. p. 165—168° (600 mg.). The mother-liquors from these hydrolyses were united and the resulting material (4·26 g.) chromatographed on aluminium oxide (120 g.) prepared in benzene; elution with ether (4 × 400 c.c.) gave the diol (V*a*), m. p. 166—169° (1·70 g.). Reacetylation of the pure diol (17 g.) with acetic anhydride (80 c.c.)–pyridine (60 c.c.) for 3 hr. at 100° gave the 3α : 12α-diacetate, m. p. 112—114° (19 g.), after crystallisation from pentane (overall yield, 42%).

To avoid the large-scale use of Girard's reagent T, oxidations were carried out, in 5 runs, with 3α : 12α-diacetoxy-24 : 24-diphenylchola-20(22) : 23-diene (m. p. 138—142°) in amounts ranging from 2 to 24 g., and the resultant oils partially hydrolysed with potassium carbonate, to give crude partly crystalline products which by chromatography on aluminium oxide and elution with benzene and ether–benzene (1 : 4) yielded the 12α-monoacetate (V*b*) (yields, 48—58%), purified by conversion into the diol (V*a*). In another run 50 g. of diene gave, after partial hydrolysis, 42 g. of crude product yielding by chromatography 19 g. (65%) of the 12α-monoacetate (Vb) m. p. 203—210°.

3α : 12α-*Dihydroxy*ætio*cholane*-17β-*carboxylic Acid* (ætio*Deoxycholic Acid*) (VI*a*).—3α : 12α-Diacetoxypregnan-20-one (V*c*) (m. p. 112—114°; 7·0 g.) in dioxan (70 c.c.) at 0° was treated dropwise with an ice-cold solution of sodium hypobromite [from sodium hydroxide (9·1 g.) in water (70 c.c.) and bromine (4·20 c.c.)] during 0·75 hr., with mechanical stirring. The mixture was stirred for 3 hr. at 0—15°, excess of sodium hypobromite destroyed with sodium hydrogen sulphite, 170 c.c. of water added, and ~200 c.c. of distillate removed in a vacuum. The solution was extracted with ether; the ethereal extract, after being shaken with 2N-sodium carbonate and water, gave a neutral oil (100 mg.). The alkaline solution, alkaline extract, and washings (with addition of a little 2N-sodium hydroxide), were heated for 2 hr. at 100° to ensure hydrolysis of acetyl groups, and added dropwise with mechanical stirring to ice-cold concentrated hydrochloric acid. The precipitated acid was filtered off, washed with water, and dried; recrystallisation from acetone–methanol of a specimen gave 3α : 12α-dihydroxy*æt*iocholane-17β-carboxylic acid (VI*a*), m. p. 294—296°. The whole of the material was treated with excess of ethereal diazomethane at 0° for 1 hr. to give, after washing, etc., methyl 3α : 12α-dihydroxy-*æt*iocholane-17β-carboxylate (VI*b*), double m. p. 114—116° and 140—143° (4·06 g., 69%). Earlier runs [with 10 g. of (V*c*)] gave yields of 55%; the mother-liquors from all runs were united and by chromatography on aluminium oxide and elution with ether and chloroform–ether (1 : 1) gave further amounts of the ester, m. p. 108° and 140°.

*Methyl* 3α-*Hydroxy*-12-*oxo*ætio*chol*-9(11)-*ene*-17β-*carboxylate* (X).—(a) *Use of* 3-(*methyl succinates*). Methyl 3α : 12α-dihydroxy*æt*iocholane-17β-carboxylate (VI*b*) by the method of M. Sorkin and Reichstein (ref. j) gave the 3-(methyl succinate) (VIII*a*), m. p. 151—153°, $[\alpha]_D^{16}$ +115° ± 2° (*c*, 1·38), in 92% yield. The united mother-liquors from several runs, by chromatography, yielded further material, m. p. 147—150°.

The dimethyl ester (VIII*a*) (3·0 g.) was refluxed in acetic acid (15 c.c.) with selenium dioxide (1·5 g.) for 18 hr. with exclusion of moisture. The hot solution was filtered, and the filtrate evaporated in a vacuum. The product, dissolved in ether–chloroform, was washed with acid, alkali, and ice-water, dried, and evaporated, to give a crystalline residue, m. p. 182—195° (1·3 g.); recrystallisation from ether–methanol gave the dimethyl ester (IX*a*) as yellowish

needles, m. p. 193°, $\lambda_{max.}$ 239—240 mμ (log ε 4·15). The mother-liquors, by evaporation and chromatography on aluminium oxide with elution with ether–benzene (1 : 1), gave a small quantity of the dimethyl ester (IX*a*), m. p. 185—193° after recrystallisation from acetone–methanol. The alkaline washings by acidification and extraction with ether yielded an oil; with ethereal diazomethane this gave a crystalline yellow product (1·61 g.), which was chromatographed on aluminium oxide (50 g.). Elution with benzene (4 × 150 c.c.) and with ether–benzene (1 : 1; 3 × 150 c.c.) gave, after recrystallisation from acetone–methanol or ether–methanol, the 3-(*methyl succinate*) (IX*a*) (534 mg.) of methyl 3α-hydroxy-12-oxo*ætio*chol-9(11)-ene-17β-carboxylate as colourless needles, m. p. 190—193°, $[\alpha]_D^{18}$ +116° ± 3° (*c*. 0·59), $\lambda_{max.}$ 239 mμ (log ε 4·14) (Found, after drying at 100°/0·01 mm. for 1 hr.: C, 67·8; H, 7·9. $C_{26}H_{36}O_7$ requires C, 67·8; H, 7·9%), giving no depression with the material from the neutral fraction and no yellow colour with tetranitromethane.

The dimethyl ester (IX*a*) (400 mg.) was refluxed with 2% methanolic potassium hydroxide (20 c.c.) for 4 hr. After addition of a few drops of water and saturation with carbon dioxide, methanol was removed completely in a vacuum, and the product acidified with hydrochloric acid and extracted with ether, to give a crude crystalline product which was esterified directly with ethereal diazomethane. The crystalline product, by chromatography on aluminium oxide (12 g.) and elution with ether–benzene (1 : 1), ether, and chloroform–ether (1 : 1), gave *methyl* 3α-*hydroxy*-12-*oxo*æ*tiochol*-9(11)*ene*-17β-*carboxylate* (X) as colourless needles (from ether), m. p. 175—177°, $[\alpha]_D^{19}$ +109° ± 2° (*c*, 1·605), $\lambda_{max.}$ 242 mμ (log ε 4·10) (Found, after drying at 70°/0·01 mm. for 2 hr.: C, 72·5; H, 8·6. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), giving no yellow colour with tetranitromethane.

In subsequent larger-scale oxidations the dimethyl ester (IX*a*) was not isolated. The hot acetic acid solution (30 c.c.) obtained by oxidation of the methyl succinate (VIII*a*) (m. p. 150—152°; 9·37 g.) with selenium dioxide (3·0 g.) for 48 hr. was filtered, and the black precipitate of selenium washed with chloroform (~300 c.c.); the filtrate and washings were united and stirred rapidly with a solution of potassium chromate (6 g.) in 50% acetic acid (~200 c.c.) at 15° for 3 hr. The chloroform layer was separated, the aqueous layer was extracted with chloroform, and the united chloroform extracts were shaken with aqueous chromium trioxide at 15° for 2 hr. This procedure removed most of the colloidal selenium; the chloroform solution was washed thrice with water, dried, and evaporated. The resulting oil (8·0 g.) was dissolved in methanol (64 c.c.), a solution of sodium hydroxide (4·6 g.) in water (6·4 c.c.) added, and the mixture set aside at 15° for 2 hr. After addition of water, saturation with carbon dioxide, and removal of methanol in a vacuum, the alkaline liquid was allowed to flow slowly into a 10% solution of acetic acid (15 c.c.) at 100°. After 0·5 hr. on the steam-bath, the suspension was cooled and the precipitated needles were filtered off and dried (4·33 g.); esterification with ethereal diazomethane and crystallisation from ether gave methyl 3α-hydroxy-12-oxo*ætio*chol-9(11)-ene-17β-carboxylate (X) (3·24 g.) in needles, m. p. 176—178°. The materials from the mother-liquor, together with that obtained by ether-extraction of the aqueous acetic acid filtrate and esterification with diazomethane, by chromatography on aluminium oxide and elution with benzene–ether (1 : 1), ether, and chloroform–ether gave a further quantity (334 mg.), m. p. 174—178° (total yield, 51%).

(b) *Use of* 3α-*ethoxycarbonyloxy-derivatives*. Methyl 3α : 12α-dihydroxy*ætio*cholane-17β-carboxylate (VI*b*) (5 g., dried by azeotropic distillation with benzene and at 20°/0·01 mm. for 0·25 hr.), dissolved in dry pyridine (20 c.c.), was treated with ethyl chloroformate (4 c.c.; freshly distilled) dropwise at 0° with exclusion of moisture, and the mixture was kept at 15—20° for 17 hr. Working up gave a colourless oil, which did not crystallise, even after chromatography. After being dried at 40°/0·01 mm., this (5·8 g.) was treated in acetic acid (30 c.c.) with a 4% solution of chromium trioxide in acetic acid (40 c.c.) for 1·5 hr. at 15—20°. Excess of chromium trioxide was destroyed with methanol, and the mixture worked up to give a crystalline product, m. p. 112—120° (4·8 g.); a small portion recrystallised from methanol in long needles, double m. p. 125—130° and 150—155°. The material was purified by chromatography on aluminium oxide (150 g.) in pentane, whereby elution with benzene–pentane (1 : 1, 5 × 500 c.c.) and with benzene (6 × 500 c.c.) gave *methyl* 3α-*ethoxycarbonyloxy*-12-*oxo*æ*tiocholane*-17β-*carboxylate* (VIII*b*) (3·26 g.) as hexagonal prisms (from ether–pentane), m. p. 155—156°, $[\alpha]_D$ +138° ± 2° (*c*, 2·862) [Found, after drying at 65°/0·05 mm., for 2 hr.: C, 68·6; H, 8·6. $C_{24}H_{36}O_6$ requires C, 68·55; H, 8·6%). Further elution with ether–benzene (2 : 3; 4 × 500 c.c.) gave methyl 3 : 12-dioxo*ætio*cholane-17β-carboxylate (550 mg.), needles (from methanol), m. p. 169—171°.

The 3α-ethoxycarbonyloxy-derivative (VIII*b*) (2 g.) was refluxed in acetic acid (50 c.c.) with selenium dioxide for 18 hr., then filtered hot, and the dark red solution was evaporated completely in a vacuum. The residue was dissolved in ether, washed with acid, water, alkali, and water,

dried, and evaporated. The neutral product was dissolved in benzene, filtered through a column of aluminium oxide, and washed through with benzene and ether–benzene (1 : 1); the filtrate by evaporation yielded reddish needles, which were recrystallised several times from ether until only slightly coloured (m. p. 158—160°; 800 mg.). A sample by sublimation at 170—200°/0·05 mm. and recrystallisation from ether gave *methyl* 3α-*ethoxycarbonyloxy*-12-*oxo*-ætio*chol*-9(11)-*ene*-17β-*carboxylate* (IX*b*) as colourless needles, m. p. 160—161°, $[\alpha]_D$ +103·5° + 2° (*c*, 0·612), $\lambda_{max.}$ 239 mμ (log ε 4·07) (Found, after drying at 95°/0·05 mm. for 2 hr.: C, 68·6; H, 8·2. $C_{24}H_{34}O_6$ requires C, 68·85; H, 8·2%), giving no yellow colour with tetranitromethane. The alkaline washings were acidified with concentrated hydrochloric acid and extracted with ether; the extract was washed repeatedly with water, dried, and evaporated, to give an acidic oil (800 mg.), which was esterified with ethereal diazomethane at 0°. The product obtained by working up was chromatographed on aluminium oxide (30 g.) prepared in pentane; elution with benzene–pentane (1 : 1; 2 × 80 c.c.) and with benzene (2 × 80 c.c.) gave the ethoxycarbonyloxy-derivative (IX*b*) (210 mg.), m. p. 160—161° after recrystallisation from ether (total yield, 50%).

This product (210 mg.) was refluxed with 1% methanolic potassium hydroxide (20 c.c.) for 1·5 hr.; after addition of a little water and saturation with carbon dioxide, methanol was removed completely in a vacuum, and the residue acidified and extracted with ether, to give a crystalline product, which was esterified by treatment with ethereal diazomethane at 0°. The resulting ester was chromatographed on aluminium oxide (5 g.) prepared in pentane, whereby elution with benzene, ether–benzene mixtures, and ether (20-c.c. eluates) gave the methyl ester (X) (158 mg.), m. p. 174° after recrystallisation from ether.

*Methyl* 3α-*Hydroxy*ætio*chol*-9(11)-*ene*-17β-*carboxylate* (XII*a*).—Methyl 3α-hydroxy-12-oxoætiochol-9(11)-ene-17β-carboxylate (X) (m. p. 175—176°; 4·95 g.) was dissolved in pure dry chloroform (5 c.c.), ethanedithiol (6 c.c.) added, and the mixture cooled to −15° and treated with dry hydrogen chloride (~300 c.c.) with exclusion of moisture. After 16 hr. at 0°, the mixture was neutralised with solid sodium carbonate and extracted with ether. The ethereal extract was washed with ice-cold 5N-sodium hydroxide, water, 2N-hydrochloric acid, and water, dried, and evaporated. Recrystallisation from ether gave square plates of *methyl* 12-(*ethylenedithio*)-3α-*hydroxy*ætio*chol*-9(11)-*ene*-17β-*carboxylate* (XI) (3·88 g.), m. p. 177—178° (Found, after drying at 65°/0·02 mm. for 2 hr.: S, 15·25. $C_{23}H_{34}O_3S_2$ requires S, 15·2%); a second crop (791 mg.), m. p. 175°, and a third crop (653 mg.), m. p. 174°, were obtained, whilst the mother-liquors gave material (625 mg.) which by chromatography on aluminium oxide (20 g.) and elution with ether–benzene (1 : 4, 3 × 60 c.c.; and 1 : 1, 3 × 60 c.c.) gave a further quantity (320 mg.), m. p. 172—176° after recrystallisation from ether (total yield, 94%).

The pure dithioketal (XI) (2·20 g.) was refluxed with W-7 Raney nickel (15 g.; Mozingo *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1013) in pure dry ethanol (100 c.c.) for 7 hr. After being kept overnight at 15—20°, the solution was filtered through aluminium oxide on a sintered-glass funnel and evaporated in a vacuum. Crystallisation from pentane gave *methyl* 3α-*hydroxy*-ætio*chol*-9(11)-*ene*-17β-*carboxylate* (XII*a*) as needles (1·69 g., 94%), m. p. 131—132°, $[\alpha]_D^{19}$ +69° ± 2° (*c*, 1·79) (Found, after drying at 70°/0·02 mm. for 2 hr.: C, 75·95; H, 9·55. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%), giving a yellow colour with tetranitromethane–chloroform. Lardon and Reichstein (ref. l.) record double m. p. 102° and 124° for a crude product. The material (850 mg.) from the mother-liquors of this and other runs, by chromatography on aluminium oxide and elution with ether–benzene (1 : 5, 1 : 1), gave a further quantity (437 mg.) of the hydroxy-ester (XII*a*), m. p. 125—130°. Acetic anhydride–pyridine at 20° gave the acetoxy-ester (XII*b*) as prismatic needles from ether–pentane, with partial transformation at 126° into thin needles, m. p. 132°; this had m. p. 132—134°, remelting at 134°, when mixed with Lardon and Reichstein's preparation (ref. l.), and 132—134°, remelting at 134—135°, with that of Heymann and Fieser (ref. m.).

*Methyl* 3-*Oxo*ætio*chol*-9(11)-*ene*-17β-*carboxylate* (XIII).—(*a*) Methyl 3α-hydroxy*ætio*chol-9(11)-ene-17β-carboxylate (XII*a*) (m. p. 126—130°; 500 mg.), dissolved in *tert.*-butanol (10 c.c.), was treated with *N*-bromoacetamide (386 mg.), water (0·5 c.c.), and pyridine (0·75 c.c.), and the mixture kept at 15° for 16 hr. Excess of *N*-bromoacetamide was destroyed with sodium thiosulphate, and the solution evaporated in a vacuum; the product was extracted with ether, the extract washed with 2N-sodium carbonate, 2N-hydrochloric acid, and water, dried, and evaporated. The residue (m. p. 85—110°; 480 mg.) was chromatographed on aluminium oxide (15 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 3 × 50 c.c.) and with benzene (50 c.c.) gave methyl 3-oxoætiochol-9(11)-ene-17β-carboxylate (XIII) (200 mg.), m. p. 125—126°, $[\alpha]_D^{19}$ +56° ± 2° (*c*, 2·20), after recrystallisation from pentane (Found, after drying at 65°/0·01 mm. for 2 hr.: C, 76·35; H, 9·0. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·15%) (Lardon

and Reichstein, ref. 1., record m. p. 123°, $[\alpha]_D$ +63° in ethanol), which depressed the m. p. of the hydroxy-ester (XII*a*) to 101°; the *semicarbazone*, plates (from methanol), had m. p. 210—212° (decomp.) (Found, after drying at 75°/0·01 mm. for 1·5 hr.: N, 11·2. $C_{22}H_{33}O_3N_3$ requires N, 10·85%). Further elution with ether–benzene (1 : 4, 3 : 7, and 1 : 1) yielded unoxidised hydroxy-ester (XII*a*) (125 mg.), m. p. and mixed m. p. 125—129°. The total yield, allowing for recovered (XII*a*), was 53%. The above procedure, based on that of Kritchevsky and Gallagher (*J. Amer. Chem. Soc.*, 1951, **73**, 184), could not be completely standardised. Other runs gave yields of 35% and 40%; a four-fold increase in the quantity of pyridine and use of 250 mg. of (XII*a*), m. p. 125—130°, afforded a yield of 64%, but repetition with 1·69 g. of (XII*a*) gave only 32%. In two runs, a small amount of an unidentified substance, m. p. 240—250°, eluted with ether–benzene (1 : 9), was encountered.

(*b*) Methyl 3α-hydroxy*æ*tiochol-9(11)-ene-17β-carboxylate (XII*a*) (500 mg.), dried by repeated azeotropic distillation with toluene and dissolved in pure dry toluene, with *cyclo*hexanone (10 c.c.), and aluminium *iso*propoxide (2 g., freshly distilled at 0·01 mm.), was refluxed under anhydrous conditions for 16 hr. After removal of toluene and *cyclo*hexanone by steam-distillation, the solution was acidified with 2N-sulphuric acid and extracted with ether. The semisolid product (411 mg.) was chromatographed on aluminium oxide (12 g.) in pentane. Elution with benzene–pentane mixtures gave oils, but use of benzene (2 × 40 c.c.) and ether–benzene (1 : 9; 2 × 40 c.c.) gave methyl 3-oxo*æ*tiochol-9(11)-ene-17β-carboxylate (XIII) (82 mg.), m. p. 122° [mixed m. p. 125—127° with the specimen described under (*a*)]. After elution with ether–benzene (1 : 4; 40 c.c.) had yielded an oil (8 mg.), use of ether–benzene (3 : 7, 2 × 40 c.c.; and 1 : 1, 2 × 40 c.c.) gave unchanged hydroxy-ester (XII*a*) (76 mg.), m. p. 125—130° (20%).

*Methyl* 3-*Oxo*æ*tiochola*-4 : 9(11)-*diene*-17β-*carboxylate* (XVb).—Methyl 3-oxo*ætio*chol-9(11)-ene-17β-carboxylate (XIII) (m. p. 120—122°; 306 mg.) was treated in acetic acid, whilst cooled and shaken, with 5·76 c.c. of a 0·161M-solution of bromine in acetic acid, added dropwise at such a rate that no considerable excess of bromine was present at any time (1 hr.). Sufficient ether was added, acetic acid removed by washing with water, 2N-sodium carbonate, and water, and the ethereal solution dried and concentrated to give, by addition of pentane, the bromo-ketone (220 mg.), m. p. 135—145°, raised by recrystallisation from ether to 145—150°. A specimen by repeated recrystallisation from ether gave *methyl* 4β-*bromo*-3-*oxo*æ*tiochol*-9(11)-*ene*-17β-*carboxylate* (XIV) in plates, m. p. 151—154°, $[\alpha]_D^{20}$ +84° ± 2° (*c*, 0·477) (Found, after drying at 50°/0·01 mm. for 3 hr.: Br, 19·8. $C_{21}H_{29}O_3Br$ requires Br, 19·5%). The residue from this and other brominations, by reduction with zinc–acetic acid at 100° for 1 hr., furnished material which on chromatography gave the pure oxo-ester (XIII), m. p. 119—123°.

The 4β-bromo-ester (XIV) (m. p. 149—153°; 85 mg.) was treated in acetic acid (8 c.c.) with 2 : 4-dinitrophenylhydrazine (25 mg.) and anhydrous potassium acetate (12 mg.) at 65° in nitrogen for 1 hr. The red solution was evaporated in a vacuum, and the residue dissolved in chloroform; pyruvic acid (1·5 c.c.) and water (0·8 c.c.) were added and the mixture was kept at 65—70° in nitrogen. After 1 hr. and then 2 hr. pyruvic acid (0·8 c.c.) was added, and after 5 hr. the yellow-brown solution was cooled and extracted with ether. The extract was well washed with 2N-sodium carbonate and water, dried, and evaporated, to give a yellow oil (85 mg.), which was chromatographed on aluminium oxide (2·5 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 3 × 10 c.c.) and benzene (2 × 10 c.c.) gave crystalline fractions, m. p. ~100°, which were united and, recrystallised twice from ether–pentane (1 : 4), gave the 3-oxo-4 : 9(11)-diene-ester (XV*b*) as rods, m. p. 99—102°, $\lambda_{max.}$ 240 mμ (log ε 4·07).

Alternatively, the 4β-bromo-ester (XIV) (m. p. 146°; 100 mg.) in acetic acid (10 c.c.) was treated similarly with semicarbazide acetate [prepared by grinding together semicarbazide hydrochloride (75 mg.) and sodium acetate trihydrate (120 mg.) with a few drops of water and filtration]. After exchange with pyruvic acid (3 c.c.), the product was isolated in the usual way and crystallised partially by scratching (75 mg.). Chromatography as under (*a*) (p. 2990) gave the 3-oxo-4 : 9(11)-diene-ester (23 mg.) (XV*b*) as rods [from ether–pentane (1 : 4)], m. p. 100—102°. Recrystallisation from ether–pentane gave *methyl* 3-*oxo*æ*tiochola*-4 : 9(11)-*diene*-17β-*carboxylate*, (XV*b*), m. p. 104—105°, $[\alpha]_D^{20}$ +132° ± 2° (Found, after drying at 50°/0·02 mm. for 4 hr.: C, 76·7; H, 8·55. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%). In a repetition, (XIV) (320 mg.) gave (XV*b*) (75 mg.), which was hydrolysed with hot 4% methanolic potassium hydroxide (2 c.c.) for 2 hr. After being worked up in the usual way, the crystalline acid fraction (65 mg.) was recrystallised from acetone–pentane, to give 3-oxo*ætio*chola-4 : 9(11)-diene-17β-carboxylic acid (XV*a*) as prisms m. p. 240—250° (decomp.).

21-*Acetoxypregna*-4 : 9(11)-*diene*-3 : 20-*dione* (II*b*).—3-Oxo*ætio*chola-4 : 9(11)-diene-17β-carb-

oxylic acid (XV*a*) (63 mg.) in benzene was treated with oxalyl chloride (50 mg.), and the mixture shaken for 0·5 hr. at 15—20° and set aside for 1 hr. Benzene and excess of oxalyl chloride were removed at 35—40°/10 mm., then, thrice, the residual yellow oil was dissolved in benzene and the benzene evaporated in a vacuum. The acid chloride, dissolved in ether–benzene (1 : 1, 5 c.c.), was treated with dry ethereal diazomethane at −5° for 1 hr.; evaporation furnished the diazo-ketone as an oil which solidified when rubbed with acetone–pentane. It was refluxed in acetic acid (5 c.c.) for 5 min. Acetic acid was removed in a vacuum, and the residue dissolved in ether, washed with water, 2N-sodium carbonate (twice), and water (thrice), and dried, and the solution evaporated. The resulting oil (44 mg.) solidified on trituration with ether–pentane and was chromatographed on neutralised aluminium oxide (1 g.) in pentane, with 5-c.c. eluates. Elution with pentane and benzene–pentane gave no material, whilst benzene–pentane yielded only oils; elution with benzene, and ether–benzene (1 : 19) gave material which crystallised when moistened with pentane and seeded with 21-acetoxypregna-4 : 9(11)-diene-3 : 20-dione (II). These fractions were united and sublimed at 180°/0·01 mm.; the sublimate (20 mg.), which crystallised on nucleation, was recrystallised from ether–pentane, to give (II) as prisms, m. p. and mixed m. p. 159°, giving a yellow colour with tetranitromethane and reducing ammoniacal silver solution immediately at 20°, and yielding an orange colour with concentrated sulphuric (green fluoresence against a dark background). The infra-red spectrum [in $CS_2$: bands at 1230 and 1756 (21-acetate), 1730 (20-carbonyl), 1677 (4 : 5-unsaturated 3-ketone), 804 and 823 cm.$^{-1}$ (>CR:CH·)] was identical with that of a genuine specimen prepared from corticosterone acetate.

*Degradation of* 21-*Acetoxypregna*-4 : 9(11)-*diene*-3 : 20-*dione* (II) *to Methyl* 3-*Oxo*æ*tiochola*-4 : 9(11)-*diene*-17β-*carboxylate* (XV*b*).—The dione (II) (m. p. 158—159°; 25 mg.), in methanol (2·5 c.c.) was hydrolysed by treatment with potassium hydrogen carbonate (25 mg.) in water (0·5 c.c.) at 20° for 16 hr. (cf. Reichstein and von Euw, *Helv. Chim. Acta*, 1938, **21**, 1181); addition of a little water and removal of methanol in a vacuum gave the crude hydroxy-dione (II*a*) (19 mg.), which was oxidised in dioxan (2 c.c.; freshly distilled over sodium) with periodic acid (25 mg.) in water (0·5 c.c.) at 20° for 16 hr. (ref. q; cf. Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925). After removal of some dioxan in a vacuum, acidification gave a precipitate which was extracted with ether; the extract was washed with water, dried, and evaporated to give a solid acid, which was esterified with ethereal diazomethane at 0°. The product, by chromatography on aluminium oxide and elution with benzene, gave an oil (10 mg.) which gradually crystallised (m. p. 95—98°) and was sublimed at 100°/0·01 mm.; the crystalline sublimate, by recrystallisation from ether–pentane gave methyl 3-oxo*ætio*chola-4 : 9(11)-diene-17β-carboxylate (XV*b*), m. p. and mixed m. p. 105°.

*Degradation of Corticosterone* (I*a*) *to Methyl* 3-*Oxo*æ*tiochola*-4 : 9(11)-*diene*-17β-*carboxylate* (XV*b*).—Corticosterone (I*a*) (m. p. 178—180°; 150 mg.) was oxidised with periodic acid at 20° to 11β-hydroxy-3-oxo*ætio*chol-4-ene-17β-carboxylic acid, m. p. 253—255° (decomp.), according to the directions of von Euw and Reichstein (ref. q), and converted into the methyl ester with ethereal diazomethane at 0°. This (m. p. 180—182°; 100 mg.) was refluxed with concentrated hydrochloric acid–acetic acid (1 : 9; 1 c.c.) for 0·5 hr.; the solution was evaporated in a vacuum, and the residue thoroughly dried by repeated azeotropic distillation with benzene and esterified with ethereal diazomethane at 0°. The resulting oil (100 mg.) was chromatographed on aluminium oxide (3 g.) in pentane, with 10-c.c. eluates. Elution with benzene–pentane (4 : 1) (fraction 14) and benzene (fractions 15—19) gave material, m. p. 95—102°, which was united and recrystallised from ether–pentane to give methyl 3-oxo*ætio*chola-4 : 9(11)-diene-17β-carboxylate (XV*b*) (23 mg.), m. p. 103°, giving no depression by admixture with a synthetic specimen, m. p. 104—105°. Elution with benzene (fractions 20—23) and with ether–benzene (1 : 49 and 1 : 19) (fractions 24, 25) gave partly crystalline material (25 mg.). Further elution with ether–benzene (1 : 9, 1 : 4, 3 : 7, 2 : 3, and 1 : 1) (fractions 26—30) gave material (45 mg.), m. p. 182° after recrystallisation from acetone–ether, consisting of the unchanged 11β-hydroxy-ester.

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## 594. *The Retardation of Benzaldehyde Autoxidation. Part V.* The Effects of Some Quinones.*

By J. R. Dunn and William A. Waters.

A kinetic study has been made of the retarding actions of 15 quinones on the benzoyl peroxide-initiated autoxidation of benzaldehyde. Only quinones of high oxidation–reduction potential are effective retarding agents, but correlations between redox potentials and retarding ability are satisfactory only if applied to substances of similar structural type. Again, the activation energy of the chain-ending process cannot be correlated with the redox potential of the quinone used.

The preceding papers of this series (*J.*, 1952, 2420, 2427, 2432) showed that when 2 : 6 : 1-xylenol was used as a retarder of the autoxidation of benzaldehyde it was slowly oxidised to 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone and then converted into 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-dibenzoyloxydiphenyl by the addition of benzoyl radicals to the oxygen atoms of the quinone. By this final action the quinone acted very effectively as a chain-stopping agent, and it was therefore decided to make a more comprehensive study of this action of quinones.

Though the relative efficacies of substituted phenols in inhibiting the autoxidations of hydrocarbons have been examined extensively in technical laboratories (Egloff, Morrell, Lowry, and Dryer, *Ind. Eng. Chem.*, 1932, **24**, 1375; 1933, **25**, 804; Rosenwald and Hoatson, *ibid.*, 1949, **41**, 914; Rosenwald, Hoatson, and Chenicek, *ibid.*, 1950, **42**, 162; Bolland and ten Have, *Discuss. Faraday Soc.*, 1947, **2**, 252) much less attention has been paid to the inhibiting powers of the quinones which may be derived from them. Milas (*Proc. Nat. Acad. Sci.*, 1929, **15**, 596; *Chem. Reviews*, 1932, **10**, 295) has reported that both *p*-benzoquinone and anthraquinone inhibit the autoxidation of anethole, Täufel and Arens (*Fette und Seifen*, 1944, **51**, 307; *Chem. Abs.*, 1950, **44**, 7567) have compared the efficiencies of a series of quinones in preventing the autoxidation of fats, and several workers have used quinones to inhibit vinyl polymerisation, but only by our previous work was the nature of the chain-stopping reaction made evident.

As the outcome of their studies of the inhibition of ethyl linoleate oxidation by quinols, Bolland and ten Have (*loc. cit.*) concluded that there was a linear relation between the chain-stopping power of a quinol and the oxidation–reduction potential for its reversible oxidation to a quinone, yet Egloff and his colleagues (*loc. cit.*) from the more cursory examination of many more phenols, had decided that a general relation between inhibiting actions and redox potentials of organic compounds could not be established. Dost (*Rec. Trav. chim.*, 1952, **71**, 857), however, concluded that the dehydrogenating powers of quinones were related to their redox potentials. In this connection Lopez Aparicio and Waters (*J.*, 1952, 4666) found that the ease of free-radical addition to the oxygen atoms of quinones could, in part, be correlated with their redox potentials, though steric effects of vicinal substituents were also significant. They pointed out that at most only approximate correlation between the free-radical reactivities of quinones and their redox potentials can be hoped for, since this is an attempt to relate the velocities of the irreversible reactions (1) and (2) with the equilibrium constants of the reversible systems (3) and (4):

(1) $Ph{\cdot}CO{\cdot} + Q \longrightarrow Ph{\cdot}CO{\cdot}Q{\cdot}$ (3) $Q + e + H^+ \rightleftharpoons {\cdot}QH$

(2) $Ph{\cdot}CO{\cdot} + {\cdot}Q{\cdot}COPh \longrightarrow Ph{\cdot}CO{\cdot}Q{\cdot}COPh$ (4) $HQ{\cdot} + e + H^+ \rightleftharpoons H_2Q$

Again, the retarding action of a quinone depends initially on the velocity of reaction (1), which yields a semiquinone radical, whilst the measurement of a redox potential does not discriminate between the consecutive stages (3) and (4) of the reduction process.

Preliminary tests showed that only quinones of high redox potential were effective retarders of the benzoyl peroxide-initiated autoxidation of benzaldehyde, and we have therefore studied quinones of this group, including substituted 4 : 4′-diphenoquinones and

* Part IV, *J.*, 1952, 2432.

4 : 4′-stilbenequinones which (i) have particularly high redox potentials and (ii) are the probable intermediate products from those alkylated monohydric phenols which have been found to be the most effective inhibitors of hydrocarbon autoxidation (compare Cosgrove and Waters, *J.*, 1951, 1726). As Table 1 shows, the alkylated derivatives of *p*-cresol which could on oxidation yield derivatives of 4 : 4′-stilbenequinone, are better inhibitors of autoxidation of cracked "gasoline" than their respective isomers.

TABLE 1. *Relative efficiencies of alkylated phenols as inhibitors of hydrocarbon autoxidation* (based on the data of Rosenwald, Hoatson, and Chenicek, *loc. cit.*).

| Substituent groups (OH = 1) | Relative efficiency | Substituent groups (OH = 1) | Relative efficiency | Substituent groups (OH = 1) | Relative efficiency |
|---|---|---|---|---|---|
| 2-Bu$^n$, 4-Me ..... | 19 | 6-Bu$^t$, 2 : 4-Me$_2$ ..... | (100) | 4-Bu$^s$, 2-Me ..... | 8 |
| 2-Bu$^i$, 4-Me ..... | 19 | 2 : 6-Bu$^t_2$, 4-Me ..... | 59 | 4-Bu$^t$, 2-Me ..... | 13 |
| 2-Bu$^s$, 4-Me ..... | 26 | 4-Bu$^n$, 2-Me ..... | 17 | 4-Bu$^t$, 2 : 6-Me$_2$ ..... | 12 |
| 2-Bu$^t$, 4-Me ..... | 42 | 4-Bu$^i$, 2-Me ..... | 12 | 2 : 4-Bu$^t_2$, 6-Me ..... | 28 |

Our experimental procedure has been that described in Parts I—III (*locc. cit.*), and since the initial rate of autoxidation was regularly found to be proportional to the benzoyl peroxide concentration of the reaction mixture and to (1/[Quinone] — constant) (see Table 4), where the constant is always very small and often zero, we consider that in all cases the retarding action can be explained by the interventions of reactions (1) and (2) above (see Part II, *J.*, 1952, 2427). The minute constants referred to above would be explicable if traces of some of the quinones were being destroyed by an independent zero-order reaction, and possibly this may be due to an initial trace of perbenzoic acid, or other unidentified impurity in the reaction mixture, for the magnitude of the constant, though not that of the [Quinone]/(Inverse Rate) ratio, did vary with the batch of benzaldehyde used.

The relative retarding powers of the selected quinones have been expressed in col. 2 of Table 2 as the reciprocal of the number of moles of quinone required to reduce to a value of 1 ml. per minute (corrected to N.T.P.) the rate of oxygen uptake at 60° of a 10-ml. sample of benzaldehyde containing 1·5 g. of benzoic acid and 0·05 g. of benzoyl peroxide catalyst.

TABLE 2. *Efficiencies of quinones as retarders of the benzoyl peroxide-catalysed autoxidation of benzaldehyde.*

| Quinone | Efficiency ($10^4$/M) | $\log_{10}$ efficiency | $E_{overall}$ (kcal.) | Redox potential, volt (+) |
|---|---|---|---|---|
| *p*-Benzoquinone ..... | 4·03 ± 0·14 | 0·6053 | 24·5 | 0·711 |
| Toluquinone ..... | 5·89 ± 0·085 | 0·7701 | — | 0·653 |
| *p*-Xyloquinone ..... | 4·61 ± 0·18 | 0·6607 | — | 0·597 |
| 2 : 5-Diethoxybenzoquinone ..... | 2·71 ± 0·18 | 0·4330 | — | 0·480 |
| Chloranil ..... | 81·8 ± 2·2 | 1·1928 | 27·6 ± 1·0 | 0·703 |
| 1 : 4-Naphthaquinone ..... | 5·37 ± 0·11 | 0·7300 | — | 0·492 |
| 2-Methyl-1 : 4-naphthaquinone ..... | 3·51 ± 0·07 | 0·5453 | 27·8 ± 0·9 | 0·422 |
| Phenanthraquinone ..... | 13·0 ± 0·6 | 1·1139 | 22·8 ± 0·2 | 0·471 |
| Chrysenequinone ..... | 11·2 ± 0·3 | 1·0492 | 25·2 ± 0·6 | 0·465 |
| 4 : 4′-Diphenoquinone ..... | 1310·0 ± 22 | 3·1173 | 28·0 | 0·954 |
| 3 : 3′-Dimethyldiphenoquinone ..... | 812·0 ± 23 | 2·9076 | — | (0·84) |
| 3 : 3′ : 5 : 5′-Tetramethyldiphenoquinone ..... | 227·0 ± 3·0 | 2·3560 | 27·0 | (0·73) |
| 3 : 5 : 3′ : 5′-Tetramethyl-4 : 4′-stilbenequinone | 356 ± 8·5 | 2·5514 | 26·4 ± 0·9 | (0·63) |
| 5 : 5′-Di-*tert.*-butyl-3 : 3′-dimethylstilbenequinone ..... | 160 ± 2·0 | 2·2041 | — | (0·58) |
| 3 : 5 : 3′ : 5′-Tetra-*tert.*-butylstilbenequinone ... | 104 ± 3·5 | 2·0176 | 23·5 | (0·54) |

Col. 5 of Table 2 gives the available values of the redox potentials of the quinones, as measured at 25° in ethanol containing N-hydrogen chloride. Unfortunately, the substituted diphenoquinones and stilbenequinones are too sparingly soluble in this solvent for accurate potential determination to be possible. Consequently, the redox potentials given in parentheses are calculated from the recorded redox potentials of unsubstituted 4 : 4′-diphenoquinone and 4 : 4′-stilbenequinone on the assumption that the alkyl substituents lower these potentials by the same amount as they do in the *p*-benzoquinone series. The relevent data have been taken from the measurements of Conant and Fieser (*J. Amer. Chem.*

*Soc.*, 1923, **45**, 2208; 1924, **46**, 858; Fieser, *ibid.*, 1930, **52**, 5204) and of Lopez Aparicio and Waters (*loc. cit.*), but the computed potentials for the *tert.*-butyl-substituted compounds may well be too high since the only available reference compound is 2 : 5-di-*tert.*-butyl-1 : 4-benzoquinone which has only one alkyl group *ortho* to each quinonoid oxygen.

It is clear from Table 2 that there is no general relation between the redox potential of a quinone and its efficiency as an inhibitor, or to the logarithm of this quantity. However, although *p*-benzoquinone is an exception, the inhibiting powers of quinones of similar ring structure do appear to increase with increasing redox potential.

In accordance with the results of Wittig and Pieper (*Annalen*, 1947, **558**, 207), chloranil is a much better inhibitor than is benzoquinone, although its redox potential in alcohol is somewhat less. However, benzaldehyde is a much less polar solvent than ethanol, and Kvalnes (*J. Amer. Chem. Soc.*, 1934, **56**, 667) has found that the redox potential of chloranil in benzene, which may be a more comparable solvent, is 0·742 v when referred to 0·711 v for benzoquinone in this solvent. But even when due allowance is made for the possible higher redox potential of chloranil, its efficiency as an inhibitor is still very high. This may be attributed to the combined inductive effect of four chlorine atoms which, by withdrawing electrons from the ring system, reduce the electron density at the quinonoid oxygen atoms and thereby increase their affinity for free radicals.

We would suggest that, within any one group of aromatic compounds of similar nuclear type, correlations between inhibitor efficiency and redox potential may be due to the fact that substituent groups will have similar effects upon both types of measurement. Alkyl groups would be expected to lower the inhibitor efficiencies of quinones, since they will increase the electron availability in the nucleus and so will lower the (electrophilic) affinity of the quinonoid oxygens for free radicals : in the phenol series the reverse will be true (see Table 1) since the alkyl groups will then, by electron donation, facilitate hydrogen-atom release. Evidently the alkylation of both positions *ortho* to the quinonoid oxygen atoms lowers the inhibitor efficiency by a relatively greater amount than the substitution of only one *ortho*-position, and this may be attributed to steric hindrance of the attack by the bulky benzoyl group (equation 1). Again, in the stilbenequinone series the replacement of methyl by *tert.*-butyl groups leads to a further marked decrease in inhibitor efficiency, though the corresponding change of redox potential is small.

When quinones of different aromatic nuclei are compared it becomes evident that there is no pervading connection between redox potential and inhibiting power. Tetramethyldiphenoquinone and benzoquinone have closely similar redox potentials, yet the former is 50 times more efficient as an inhibitor. Tetramethylstilbenequinone, which should have a redox potential about 0·1 v lower than that of tetramethyldiphenoquinone, is a slightly more efficient inhibitor. Again, the retarding powers of *p*-benzoquinone and 1 : 4-naphthaquinone are much more alike than their redox potentials would indicate, and the efficiencies of phenanthraquinone and chrysenequinone are much greater than would have been expected.

Two theoretical considerations are relevent to this subject : (*a*) The redox potential of a quinone is a measure of its free energy of reduction, and will only be a corresponding measure of its heat of reduction within a series of compounds in which the entropy of reduction can be regarded as constant. According to Evans (*Trans. Faraday Soc.*, 1946, **42**, 113), this will be so for substances of the same structural type, but it is most unlikely that the entropies of reduction of benzoquinone and diphenoquinone will be the same, since 4 : 4′-dihydroxydiphenyl is capable of free rotation about the bond between the two aromatic rings. (*b*) The efficiency of radical capture by a quinone is due essentially to reaction (1) (p. 2993), *i.e.*, to the reduction of a quinone to a semiquinone radical. Although for quinones of similar structure the free-energy change for this step may be a constant proportion of the free-energy change for the complete two-electron reduction, this is certainly not true for quinones of different series, as has been shown by Fieser (*loc. cit.*). Unfortunately, he determined the free-energy change for the first stages of the reductions of only benzoquinone and diphenoquinone, and data for the other quinones now examined are not available.

Col. 4 of Table 2 gives the overall activation energies for a number of the quinone-inhibited autoxidations of benzaldehyde as computed, by the Arrhenius equation, from

3 or 4 sets of measurements in the temperature range 50—75°. For the chain reaction concerned in this autoxidation:

$$E_{\text{overall}} = E_{\text{initiation}} + E_{\text{propagation}} - E_{\text{chain-ending}}$$

$E_{\text{propagation}}$ refers to the reaction

$$\text{Ph·CO·O·O·} + \text{Ph·CHO} \longrightarrow \text{Ph·CO·O·OH} + \text{Ph·CO·}$$

which has been found by Ingles and Melville (*Proc. Roy. Soc.*, 1953, *A*, **218**, 163, 175) to be $1{\cdot}8 \pm 0{\cdot}5$ kcal. $E_{\text{initiation}}$ can be taken as the activation energy of benzoyl peroxide decomposition, which, though it has not been studied in benzaldehyde, was found by Bawn and Mellish (*Trans. Faraday Soc.*, 1951, **47**, 1216) to be 29·6 kcal. in a number of other solvents. From these figures we derive the values given in Table 3 for the activation energies of chain termination. Clearly, these activation energies cannot be correlated mathematically either with redox potentials or with inhibiting efficiencies, as would be the case if entropy factors remained constant.

TABLE 3. *Activation energies of inhibition of benzaldehyde autoxidation by quinones.*

| Quinone | *E* (kcal.) | Efficiency | Redox potential, v. |
|---|---|---|---|
| Diphenoquinone | 3·0 | 1310 | 0·954 |
| 2-Methyl-1 : 4-naphthaquinone | 3·0 | 3·51 | 0·422 |
| Chloranil | 3·0 | 81·8 | 0·703 |
| 3 : 5 : 3′ : 5′-Tetramethyldiphenoquinone | 4·0 | 227·0 | (0·73) |
| 3 : 5 : 3′ : 5′-Tetramethylstilbenequinone | 5·0 | 356·0 | (0·63) |
| Chrysenequinone | 6·0 | 11·2 | 0·465 |
| *p*-Benzoquinone | 7·0 | 4·03 | 0·711 |
| 3 : 5 : 3′ : 5′-Tetra-*tert.*-butylstilbenequinone | 8·0 | 104·0 | (0·58) |
| Phenanthraquinone | 9·0 | 13·0 | 0·471 |

Throughout, the computed standard deviations of our measurements are so low that, although our actual figures for activation energies and inhibitor efficiencies may be subject to systematic errors associated with either the technique or the theoretical computations, yet the relative orders of the figures of Table 3 can be relied on unless minute traces of impurities (*e.g.*, quinols) in certain of the quinones have an overwhelming effect even when present in traces too small to have been revealed by our criteria for purity.

Thus from our results we conclude, in general agreement with Egloff and his colleagues, that there is no *general* correlation between redox potentials and inhibitory effect of quinones on benzaldehyde autoxidation. There seems, however, to be some correlation between inhibitor efficiency and redox potential amongst quinones of the same structural type, and we suggest that this may be due to the fact that the "induced polarity" of substituent groups would affect both molecular properties in a similar way.

## EXPERIMENTAL

Initial rates of oxygen uptake were measured as described by Waters and Wickham-Jones (Part II, *loc. cit.*), using 10-ml. samples of benzaldehyde containing 1·5 g. of benzoic acid. Both the benzaldehyde and the benzoyl peroxide were purified by their method. The inhibitor efficiency of each quinone, as previously defined (p. 2994), was calculated as

$$\frac{\text{g.-mol. weight of quinone}}{(\text{mg. of quinone taken}) \times (\text{O}_2 \text{ uptake rate in ml./min. at } 60°)}$$

In Table 4, *n* gives the number of observations, upon different weights of quinones, from which the product 1/(mg. of quinone × absorption rate) of the following column has been calculated. The standard deviations for these products have been computed by Birge's method (*Phys. Review*, 1932, **40**, 207). Except for the 3 diphenoquinones marked *, the data refer to mixtures containing 0·0500 g. of benzoyl peroxide catalyst. For these diphenoquinones, however, measurements were made with 0·2500 g. of benzoyl peroxide, but since with each of them it was found experimentally that the oxygen uptake rate was directly proportional to the first power of the benzoyl peroxide concentration (see Part III) the experimental data can all be reduced to the standard values used in Tables 2 and 3.

*Preparation and Purification of Quinones.*—*p*-Benzoquinone was steam-distilled and then crystallised from light petroleum to constant m. p. (112·5°). *p*-Xyloquinone was prepared from *p*-xylidene sulphate as described by Kehrmann and Stiller (*Ber.*, 1912, **45**, 3348), distilled in steam, and dried in a vacuum; it had m. p. 123°. Toluquinone, 2 : 5-diethoxybenzoquinone, and chloranil were pure materials that had been prepared by Dr. Lopez Aparicio. 1 : 4-Naphthaquinone, prepared by Conant and Freeman's method (*Org. Synth.*, Coll. Vol. I, p. 376),

TABLE 4.

| Quinone | Temp., °K | *n* | 1/($O_2$ uptake rate) (mg. quinone taken) | Intercept on concn. axis (mg. quinone) |
|---|---|---|---|---|
| Benzoquinone | 328 | 6 | 0·0667 ± 0·0022 | — |
| | 333 | 9 | 0·0373 ± 0·0013 | — |
| | 338 | 6 | 0·0232 ± 0·0008 | — |
| Toluquinone | 333 | 10 | 0·0483 ± 0·0007 | — |
| *p*-Xyloquinone | 333 | 9 | 0·0340 ± 0·0013 | — |
| Chloranil | 333 | 10 | 0·3328 ± 0·0088 | 0·0203 ± 0·0007 |
| | 338 | 5 | 0·1750 ± 0·0064 | 0·0203 ± 0·0009 |
| | 343 | 5 | 0·1000 ± 0·0051 | 0·0228 ± 0·0007 |
| | 348 | 5 | 0·0575 ± 0·0048 | 0·0228 ± 0·0007 |
| 2 : 5-Diethoxybenzoquinone | 333 | 8 | 0·0138 ± 0·0009 | 0·0291 ± 0·0002 |
| 1 : 4-Naphthaquinone | 333 | 11 | 0·0340 ± 0·0007 | — |
| 2-Methyl-1 : 4-naphthaquinone | 328 | 6 | 0·0366 ± 0·0004 | — |
| | 333 | 8 | 0·0204 ± 0·0004 | — |
| | 338 | 6 | 0·0104 ± 0·0003 | — |
| | 343 | 6 | 0·0055 ± 0·0002 | — |
| Phenanthraquinone | 328 | 6 | 0·1075 ± 0·0017 | 0·0053 ± 0·0002 |
| | 333 | 7 | 0·0653 ± 0·0028 | 0·0068 ± 0·0004 |
| | 338 | 6 | 0·0400 ± 0·0010 | 0·0082 ± 0·0002 |
| | 343 | 6 | 0·0236 ± 0·0003 | 0·0100 ± 0·0001 |
| Chrysenequinone | 328 | 6 | 0·0764 ± 0·0025 | — |
| | 333 | 10 | 0·0436 ± 0·0012 | — |
| | 339 | 6 | 0·0216 ± 0·0004 | — |
| | 343 | 6 | 0·0144 ± 0·0003 | — |
| * 4 : 4′-Diphenoquinone | 328 | 6 | 2·670 ± 0·093 | 0·0011 ± 0·0007 |
| | 333 | 8 | 1·420 ± 0·0243 | 0·0028 ± 0·0004 |
| | 338 | 7 | 0·725 ± 0·031 | 0·0047 ± 0·0006 |
| * 3 : 3′-Dimethyl-4 : 4′-diphenoquinone | 333 | 9 | 0·766 ± 0·022 | 0·0025 ± 0·0002 |
| * 3 : 3′ : 5 : 5′-Tetramethyl-4 : 4′-diphenoquinone | 333 | 10 | 0·189 ± 0·0025 | — |
| | 338 | 5 | 0·1058 ± 0·0025 | — |
| | 343 | 5 | 0·0562 ± 0·0018 | — |
| 3 : 5 : 3′ : 5′-Tetramethyl-4 : 4′-stilbenequinone | 333 | 9 | 1·262 ± 0·032 | 0·0019 ± 0·0004 |
| | 338 | 5 | 0·666 ± 0·057 | 0·0033 ± 0·0009 |
| | 343 | 5 | 0·381 ± 0·021 | 0·0051 ± 0·0007 |
| | 348 | 5 | 0·233 ± 0·014 | 0·0079 ± 0·0007 |
| 5 : 5′-Di-*tert.*-butyl-3 : 3′-dimethylstilbenequinone | 333 | 9 | 0·455 ± 0·006 | 0·0025 ± 0·0001 |
| 3 : 5 : 3′ : 5′-Tetra-*tert.*-butylstilbenequinone | 333 | 8 | 0·256 ± 0·0086 | 0·0104 ± 0·0001 |
| | 338 | 6 | 0·149 ± 0·0059 | 0·0127 ± 0·0003 |
| | 343 | 6 | 0·0889 ± 0·0061 | 0·0206 ± 0·0004 |

was purified by vapour distillation and dried in a vacuum (over $P_2O_5$), had m. p. 123°. 2-Methyl-1 : 4-naphthaquinone (Light & Co.) was crystallised from methanol to constant m. p. (105·5°). Phenanthraquinone, made from pure phenanthrene, was crystallised to constant m. p. (208°) from hot benzene. Chrysenequinone, prepared from chrysene by Graebe and Hönigsberger's method (*Annalen*, 1900, **311**, 262), was crystallised to constant m. p. (236°) from glacial acetic acid and dried in a vacuum.

*Diphenoquinone.* 4 : 4′-Dihydroxydiphenyl, prepared from benzidine (Hirsch, *Ber.*, 1889, **22**, 1335), was oxidised to the quinone with lead dioxide (Willstätter and Kelb, *Ber.*, 1905, **38**, 202), and the quinone crystallised from benzene; it had m. p. 160° (decomp.).

3 : 3′-*Dimethyldiphenoquinone.* 4 : 4′-Dihydroxy-3 : 3′-dimethyldiphenyl, m. p. 156°, was prepared from *o*-tolidine (Gerber, *Ber.*, 1888, **21**, 749; Hobbs, *ibid.*, p. 1067; Winston, *Amer. Chem. J.*, 1904, **31**, 119) and then oxidised to 3 : 3′-*dimethyl*-4 : 4′-*diphenoquinone* with lead

dioxide, though in poor yield. After crystallisation from benzene the quinone had m. p. 165° (decomp.) (Found: C, 78·9; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·3; H, 5·6%).

3 : 5 : 3′ : 5′-Tetramethyldiphenoquinone, m. p. 203—204° (decomp.), was prepared by Mr. R. F. Moore (see Part IV). 3 : 5 : 3′ : 5′-Tetramethyl-4 : 4′-stilbenequinone, prepared by oxidation of mesitol by silver oxide (Porter and Thurber, *J. Amer. Chem. Soc.*, 1921, **43**, 1194), was crystallised from boiling xylene; it had m. p. 218—220° (decomp.).

5 : 5′-*Di*-tert.-*butyl*-3 : 3′-*dimethyl*-4 : 4′-*stilbenequinone*. 6-*tert.*-Butyl-2 : 4-dimethylphenol (5 g.) in benzene (200 ml.) was warmed at 50° for 4 hr., with occasional shaking, with freshly prepared silver oxide (25 g.). The mixture was then heated to boiling and filtered hot, and the residue extracted with more benzene. After evaporation, the extracts left a tarry product which on trituration with a little petroleum (b. p. 100—120°) yielded an orange-red solid. This *quinone* was crystallised to constant m. p. (225°) from petroleum (b. p. 100—120°) (Found: C, 82·1; H, 8·4; $C_{24}H_{30}O_2$ requires C, 82·3; H, 8·6%).

3 : 5 : 3′ : 5′-Tetra-*tert.*-butylstilbenequinone was prepared by a similar method from 2 : 6-di-*tert.*-butyl-4-methylphenol and was crystallised to constant m. p. (302°) from petroleum. The yield was about double that of Cosgrove and Waters (*J.*, 1951, 388) who used benzoyl peroxide as the oxidiser.

We thank Dr. D. McNeil, of the Coal Tar Research Association, Gomersal, for providing us with pure specimens of the butylated phenols. One of us (J. R. D.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, May 7th*, 1953.]

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## 595. *Thia- and Dithia-alkanebis(quaternary Ammonium) Salts as Neuromuscular- and Ganglion-blocking Agents.*

By K. J. M. ANDREWS, F. BERGEL, and A. L. MORRISON.

The preparation of a number of thia- and dithia-alkane(bisquaternary ammonium) salts is described.

THE discovery that polymethylene(bisquaternary ammonium) salts exert neuromuscular- or ganglion-blocking activities, depending on the length of the polymethylene chain, made it of interest to investigate the replacement of one or more methylene groups in such compounds by a sulphur atom.

Marxer and Miescher recently (*Helv. Chim. Acta*, 1951, **34**, 924) mentioned the preparation of 3-thiapentane-1 : 5-bis(trimethylammonium iodide), and the corresponding chloride had previously been prepared by Lawson and Reid (*J. Amer. Chem. Soc.*, 1925, **47**, 2821). We prepared this iodide (Ro 3-0438) by reaction of the sodium mercaptide, dissolved in ethanol, with 2-chloroethyldimethylamine in a nitrogen atmosphere (cf. Brighton and Emmet Reid, *J. Amer. Chem. Soc.*, 1943, **65**, 438) and quaternisation of the resulting tertiary compound with methyl iodide. This reaction has proved to be general, giving high yields. However, it cannot be used for formation of the dibutyl homologue since the 4-chlorobutyldimethylamine quaternises internally very rapidly to give 1 : 1-dimethylpyrrolidinium chloride. An attempt to overcome this by the use of the method due to Gilman *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1845), *i.e.*, the reaction of 4-chlorobutyldimethylamine hydrochloride with 4-mercaptobutyldimethylamine was not successful. The 4-chlorobutyldimethylamine hydrochloride required for this attempt was prepared by the reduction of *NN*-dimethylsuccinamic acid with lithium aluminium hydride (Avison, *J. Appl. Chem.*, 1951, **1**, 469) and reaction of the resulting 4-hydroxybutyldimethylamine with thionyl chloride. The thiol was prepared by the decomposition of the thiuronium salt from the chloro-compound. However, it was evident that the reaction should be carried out with a quaternary salt and, with this in view, 4-hydroxybutyltrimethylammonium iodide was treated with thionyl chloride; a product was obtained in the form of orange-coloured needles with a high halogen content. The results obtained by Brownell and King (*J. Amer. Chem. Soc.*, 1949, **71**, 2926) on the formation of chloro-

iodates by the action of thionyl chloride on quaternary ammonium iodides suggested that this compound had the structure $Cl\cdot[CH_2]_4\cdot NMe_3\}ICl_2$. Maréchal and Bagot (*Ann. Pharm. France*, 1946, 180) have reported the preparation of 4-bromobutyltrimethylammonium bromide by the quaternisation of 1 : 4-dibromobutane with trimethylamine. We found this method to be impracticable owing to the difficulty of the separation, by crystallisation, of the mono- from the bis-ammonium compound which is formed at the same time.

Finally, 4-chlorobutyltrimethylammonium bromide, prepared from 1-bromo-4-chlorobutane (Star and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1595) and trimethylamine, was condensed with sodium sulphide to give 5-thianonane-1 : 9-bis(trimethylammonium bromide).

In a similar way, 4-thiaheptane-1 : 7-bis(triethylammonium iodide) (Ro 3-0381) was prepared from 3-chloropropyltriethylammonium iodide.

In order to study unsymmetrical thia-compounds, 5-thiaundecane-1 : 11-bis(trimethylammonium iodide) (Ro 3-0462) and 3-thiahexane-1 : 6-bis(trimethylammonium iodide) (Ro 3-0468) were prepared by the reaction of a sodium mercaptide with a chloro-compound, followed by quaternisation of the tertiary compound with methyl iodide. Since RCl and R'SH, or R'Cl and RSH, yield the same sulphide, it is preferable, and sometimes essential, to use the more stable chloro-compound.

A number of disulphides were prepared in which two methylene groups were replaced by sulphur atoms. Taichi Harada (*Bull. Chem. Soc. Japan*, 1929, **4**, 171; *Chem. Zentr.*, 1929, II, 2552) reported the preparation of 3 : 4-dithiahexane-1 : 6-bis(trimethylammonium bromide), and Renshaw, Dreisbach, Ziff, and Green (*J. Amer. Chem. Soc.*, 1938, **60**, 1765) synthesised the corresponding di-iodide and 2 : 5-dimethyl-3 : 4-dithiahexane-1 : 6-bis(trimethylammonium iodide), by air oxidation of the corresponding tertiary amino-thiols followed by quaternisation. Gilman *et al.* (*loc. cit.*) obtained similar tertiary compounds through the oxidation, with iodine, of diethyl-mercaptoethylamines and -mercaptopropylamines.

The preparation of the 3 : 4-dithiahexane-1 : 6-bis(trimethylammonium iodide), described by Renshaw *et al.* (*loc. cit.*), has been repeated, but with oxidation of the sodium mercaptides by iodine in potassium iodide solution. Also, 4 : 5-dithiaoctane-1 : 8-bis(triethylammonium iodide) (Ro 3-0384) and 5 : 6-dithiadecane-1 : 10-bis(trimethylammonium iodide) (Ro 3-0386) were prepared. The thiols were obtained by the method of Renshaw *et al.* (*loc. cit.*) and, for the preparation of Ro 3-0384, the thiol was not isolated but was oxidised directly after liberation from the thiuronium salt.

In tests upon head drop in rabbits and on the neuromuscular preparation in the cat, and also tests in man (unpublished work by Bächtold, Pellmont, and Randall; Hunter, *Brit. J. Pharmacol.*, 1953, **8**, 115) the substances with more than seven atoms between the quaternary nitrogen atoms showed predominantly neuromuscular-blocking action of the decamethonium type. The lower homologues exhibited a depressor action on cat blood pressure and blocked transmission in the cat superior cervical sympathetic ganglion (unpublished work by Bächtold, Pellmont, and Randall).

## Experimental

*Hydroxy-amines.*—4-Hydroxybutyldimethylamine was prepared by Avison's method (*J. Appl. Chem.*, 1951, **1**, 469), or by condensation of dimethylamine with 4-bromobutyl acetate (Smorgonskii and Gol'dfarb, *J. Gen. Chem.* U.S.S.R., 1940, **10**, 1113) in methanol–ether and hydrolysis of the 4-dimethylaminobutyl acetate, to give the desired hydroxy-amine in good yield.

6-*Hydroxyhexyldimethylamine.* The preparation was based on that of 1-6'-hydroxyhexylpiperidine (Avison, *loc. cit.*). Ethyl hydrogen adipate (*Org. Synth.*, **19**, 45) was converted into the acid chloride with thionyl chloride (1½ hr. on the water-bath), and this, with dimethylamine in ether, gave *ethyl* NN-*dimethyladipamate*, b. p. 102—106°/0·25 mm., $n_D^{20}$ 1·4573 (Found : C, 59·2; H, 9·1. $C_{10}H_{19}O_3N$ requires C, 59·7; H, 9·5%). Reduction with lithium aluminium hydride in ether gave 6-*hydroxyhexyldimethylamine*, b. p. 114—116°/12 mm., $n_D^{20\cdot5}$ 1·4482 (Found : N, 9·3. $C_8H_{19}ON$ requires N, 9·6%).

*Chloro-compounds.*—4-*Chlorobutydimethylamine hydrochloride.* Thionyl chloride was caused

to react with 4-hydroxybutyldimethylamine in benzene; the hygroscopic product had m. p. 118—119° (Found: N, 8·4; $Cl^-$, 20·7. Calc. for $C_6H_{15}NCl_2$: N, 8·1; $Cl^-$, 20·6%).

*6-Chlorohexyldimethylamine hydrochloride*, prepared from thionyl chloride and 6-hydroxyhexyldimethylamine in chloroform, had m. p. 110—112° (hygroscopic) (Found: N, 6·6; $Cl^-$, 18·3. $C_8H_{19}NCl_2$ requires N, 7·0; $Cl^-$, 17·7%).

3-Chloropropyldimethylamine and 3-chloropropyldiethylamine were prepared by condensing the dialkylamine with 1-bromo-3-chloropropane in ether (Marxer, *Helv. Chim. Acta*, 1941, **24**, 209E).

*4-Chlorobutyltrimethylammonium bromide.* 1-Bromo-4-chlorobutane was added to a solution of trimethylamine in benzene. The quaternisation was carried out at 45—50° for 8 hr. and a further 24 hr. at room temperature. The quaternary *salt* had m. p. 134—136° (Found: N, 6·0. $C_7H_{17}NClBr$ requires N, 6·1%).

*Thiols.*—1-Mercaptoethyldimethylamine was prepared from the chloro-compound, with the thiuronium salt as intermediate, according to the method of Clinton *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 950). The higher homologues were prepared in the same way: *3-mercaptopropyldimethylamine* had b. p. 40—41°/12 mm., $n_D^{20}$ 1·4666 (Found: N, 11·1. $C_5H_{13}NS$ requires N, 11·8%), and *4-mercaptobutyldimethylamine* had b. p. 84°/35 mm., $n_D^{21}$ 1·4677 (Found: N, 10·7. $C_6H_{15}NS$ requires N, 10·6%). 3-Mercaptopropyldiethylamine was prepared by Gilman *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1845).

*1 : 5-Bisdimethylamino-3-thiapentane.*—Sodium (1 g.) was dissolved in ethanol (25 ml.), in a nitrogen atmosphere, and 2-mercaptoethyldimethylamine (4·2 g.) was added. 2-Chloroethyldimethylamine hydrochloride (6·4 g.) was dissolved in a little water, and the free base was liberated by the addition of 30% sodium hydroxide solution at <0° and extracted with ether. The ethereal solution was dried ($Na_2SO_4$) and evaporated. The residual oil was dissolved in ethanol (20 ml.), and the solution was added to the ethanolic sodium mercaptide. Immediately a precipitate of sodium chloride was formed. The mixture was heated under reflux for 10 min. and then set aside at room temperature overnight. After removal of the precipitated sodium chloride, the filtrate was evaporated, *in vacuo*, to give a brown oil (6·9 g.). On distillation a forerun of thiol was obtained and then *1 : 5-bisdimethylamino-3-thiapentane* as a colourless oil, b. p. 58—60°/0·15 mm., $n_D^{20}$ 1·4757 (3·8 g., 54%) (Found: S, 18·1. $C_8H_{20}N_2S$ requires S, 18·2%).

*3-Thiapentane-1 : 5-bis(trimethylammonium Iodide)* (Ro 3-0438) (Marxer and Miescher, *loc. cit.*).—1 : 5-Bisdimethylamino-3-thiapentane (3 g.) in benzene (15 ml.) at 0° was treated with methyl iodide (5·3 g.) in benzene (15 ml.). Quaternisation started immediately but the mixture was kept for 24 hr. The quaternary salt, after drying, had m. p. 290° (decomp.) (7·9 g.). Recrystallisation from methanol gave colourless crystals, m. p. 298—300° (decomp.) (5·7 g., 73%) (Found: N, 5·7; S, 7·2. Calc. for $C_{10}H_{26}N_2SI_2$: N, 6·1; S, 6·9%).

*1 : 6-Bisdimethylamino-3-thiahexane.*—Sodium (0·9 g.) was dissolved in dry ethanol (30 ml.), in a nitrogen atmosphere, and 2-mercaptoethyldimethylamine (4·2 g.) in ethanol (5 ml.) was added, followed by 3-chloropropyldimethylamine (5 g.) in dry ethanol (15 ml.). Sodium chloride was immediately precipitated and the mixture was heated under reflux for ½ hr. The sodium chloride was filtered off and the filtrate was evaporated, *in vacuo*, to give an oil together with some solid. The oil was extracted with ether and, after evaporation of the ether, distilled to give *1 : 6-bisdimethylamino-3-thiahexane*, b. p. 57°/0·2 mm., $n_D^{21}$ 1·4742 (5·6 g., 74%) (Found: N, 14·9; S, 16·5. $C_9H_{22}N_2S$ requires N, 14·7; S, 16·8%).

*3-Thiahexane-1 : 6-bis(trimethylammonium Iodide)* (Ro 3-0468).—1 : 6-Bisdimethylamino-3-thiahexane (2·8 g.) in dry ether (15 ml.) at 0° was treated cautiously with methyl iodide (4·6 g.) in cold dry ether (15 ml.). Quaternisation started immediately but the mixture was kept for 15 hr. The quaternary *salt* was recrystallised from methanol, forming colourless needles (6 g., 86%), m. p. 236·5—237·5° (Found: N, 6·2; I, 53·7. $C_{11}H_{28}N_2SI_2$ requires N, 5·9; I, 53·6%).

*4-Thiapentane-1 : 7-bis(triethylammonium Iodide)* (Ro 3-0381).—(*a*) To sodium sulphide (0·8 g.) in 50% aqueous ethanol (25 ml.), 3-chloropropyltriethylammonium iodide (3·1 g.) in 50% aqueous ethanol (50 ml.) was added. The resulting solution was heated under reflux for 2 hr. After evaporation to dryness, *in vacuo*, the residue was extracted with alcohol. Evaporation and extraction with alcohol was repeated and the alcoholic solution was stored in the refrigerator. Crystals were deposited [m. p. 243—244° (decomp.)]. Recrystallised from ethanol the *di-iodide* had m. p. 257—258° (0·7 g., 25%) (Found: C, 37·1; H, 7·5. $C_{18}H_{42}N_2SI_2$ requires C, 37·8; H, 7·4%).

(*b*) Sodium (0·36 g.) in ethanol (10 ml.) was treated with diethyl-3-mercaptopropylamine (2·2 g.) in ethanol (3 ml.), and then with freshly distilled 3-chloropropyldiethylamine (2·4 g.) in nitrogen, and the whole was heated under reflux for 1 hr., filtered, and evaporated on the water-

bath *in vacuo*. The residual oil was distilled, to give 1 : 7-*bisdiethylamino*-4-*thiaheptane*, b. p. 80—81°/0·03 mm., $n_D^{21}$ 1·4730 (3·1 g., 80%) (Found : C, 64·8; H, 12·3; N, 10·7. $C_{14}H_{32}N_2S$ requires C, 64·6; H, 12·4; N, 10·8%).

This base (1·6 g.) and ethyl iodide (1·25 ml.) in ethanol (5 ml.) were heated under reflux for 6 hr. and then set aside overnight. Crystals separated from the solution and were collected by filtration [m. p. 247—249° (decomp.); 3 g., 85%]. Two recrystallisations from propanol gave colourless crystals (1·7 g.), m. p. 256—257° (decomp.), undepressed in admixture with the product from (*a*) (Found : N, 4·7; S, 5·2. $C_{18}H_{42}N_2SI_2$ requires N, 4·9; S, 5·6%).

5-*Thianonane*-1 : 9-*bis*(*trimethylammonium Bromide*) (Ro 3-0385).—To a boiling solution of sodium sulphide (3 g.) in 50% aqueous ethanol (50 ml.) 4-chlorobutyltrimethylammonium bromide (5·8 g.) in 50% aqueous ethanol (50 ml.) was added, and heating continued for 3 hr. After evaporation of the solution to dryness, *in vacuo*, the residue was extracted with alcohol (the remaining solid was shown to be sodium chloride). Evaporation and extraction with alcohol was twice repeated and the final residue was recrystallised from alcohol with the addition of ethyl acetate, followed by ether until a turbidity appeared (yield : 2·2 g., 43%; m. p. 205—220°). Two further crystallisations gave the *dibromide* (1·3 g., 25%), m. p. 232—233°, very hygroscopic colourless plates (Found : C, 40·0; H, 8·5; S, 8·0. $C_{14}H_{34}N_2SBr_2$ requires C, 39·8; H, 8·1; S, 7·6%).

1 : 11-*Bisdimethylamino*-5-*thiaundecane*.—A solution from sodium (0·5 g.), and dry ethanol (15 ml.) was treated with 4-mercaptobutyldimethylamine (2·7 g.), in ethanol (3 ml.), in a nitrogen atmosphere and then, dropwise with occasional shaking with 6-chlorohexyldimethylamine (2·75 g.; freshly liberated from its hydrochloride) in ethanol (10 ml.). There was an immediate precipitate and the reaction was completed by heating under reflux for ½ hr. Sodium chloride was filtered off and the filtrate was evaporated *in vacuo* to give an oil containing some solid. The oil was extracted with ether and, after drying ($Na_2SO_4$) of the ethereal solution and evaporation, the residual oily *base* was distilled; it had b. p. 100—105°/0·2 mm. (2·8 g., 64%) (Found : N, 10·7; S, 12·2. $C_{14}H_{32}N_2S$ requires N, 10·8; S, 12·3%)

5-*Thiaundecane*-1 : 11-*bis*(*trimethylammonium Iodide*) (Ro 3-0462).—1 : 11-Bisdimethylamino-5-thiaundecane (2·5 g.) in benzene (10 ml.) at 0° was treated with methyl iodide (3·1 g.) in benzene (5 ml.) and, after 24 hr., the solid was collected and recrystallised from ethanol. A colourless micro-crystalline *salt* was obtained, having m. p. 183—185° (4·1 g., 79%) (Found : C, 34·9; H, 6·6; N, 5·2. $C_{16}H_{38}N_2SI_2$ requires C, 35·3; H, 7·0; N, 5·2%).

3 : 4-*Dithiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*) (Ro 3-0426) (Renshaw *et al., loc. cit.*).—2-Mercaptoethyldimethylamine (3 g.) in 5N-sodium hydroxide (5·6 ml.) was treated with iodine (4·25 g.) in aqueous potassium iodide (12 g. in 60 ml.). Making the mixture strongly alkaline with 5N-sodium hydroxide precipitated an oil which, after being taken up in ether, dried ($Na_2SO_4$) and recovered, distilled at 72°/0·1 mm. (2·1 g., 70%). This was treated in dry benzene (8 ml.) with methyl iodide (2 ml.), with cooling. The quaternary salt started to crystallise immediately and, next morning, was filtered off and recrystallised from methanol (yield : 4·3 g., 88%). A further recrystallisation raised the m. p. from 236° to 240° (decomp.) (Found : C, 24·5; H, 5·3; I, 51·8. Calc. for $C_{10}H_{26}N_2S_2I_2$ : C, 24·4; H, 5·3; I, 51·6%).

1 : 8-*Bisdiethylamino*-4 : 5-*dithiaoctane* (Gilman *et al., loc. cit.*).—*S*-3-Diethylaminopropylthiuronium chloride hydrochloride (7·6 g.) was warmed in 5N-sodium hydroxide (17·4 ml.) for 20 min. at *ca.* 90°. Iodine (3·7 g.) in potassium iodide solution was then added to the solution of the liberated thiol until free iodine remained (practically all the iodine was used). After filtration, the slight excess of iodine was removed with sodium sulphite, the disulphide extracted with ether, and the ethereal solution dried (NaOH). After removal of the ether, the residual oil (3·1 g.) was distilled; it had b. p. 130—136°/0·5 mm. (2 g., 51%) (Found : C, 57·6; H, 10·5; N, 10·4. Calc. for $C_{14}H_{32}N_2S_2$ : C, 57·5; H, 11·0; N, 9·6%).

4 : 5-*Dithiaoctane*-1 : 8-*bis*(*triethylammonium Iodide*) (Ro 3-0384).—1 : 8-Bisdiethylamino-4 : 5-dithiaoctane (1 g.) in benzene (5 ml.) and ethyl iodide (1 ml.) at 45° for 3 hr. and then overnight at room temperature gave a quaternary *salt* (1 g.) which, recrystallised from ethanol, had m. p. 232° (0·85 g., 41%). Further recrystallisation raised the m. p. to 236° (Found : C, 36·0; H, 7·5; S, 10·2. $C_{18}H_{42}N_2S_2I_2$ requires C, 35·8; H, 7·0; S, 10·6%).

1 : 10-*Bisdimethylamino*-5 : 6-*dithiahexane*.—4-Mercaptobutyldimethylamine (3·9 g.) was dissolved in dilute sodium hydroxide solution, and iodine (4·9 g.) in 20% aqueous potassium iodide (100 ml.) was added. The solution was then made strongly alkaline and extracted with ether. The ethereal solution was dried ($Na_2SO_4$) and evaporated; the residual oily *base* had b. p. 110—112°/0·3 mm. (2·6 g., 67%) (Found : C, 54·7; H, 10·9; N, 10·4. $C_{12}H_{28}N_2S_2$ requires C, 54·5; H, 10·7; N, 10·6%).

5 : 6-*Dithiahexane*-1 : 10-*bis*(*trimethylammonium Iodide*) (Ro 3-0386).—1 : 10-Bisdimethylamino-5 : 6-dithiadecane (2·6 g.) in dry benzene (15 ml.) was treated with methyl iodide (1·8 ml.) with cooling and kept for 3 days. The product was then collected (m. p. 182—184°). Recrystallisation from alcohol gave colourless 5 : 6-*dithiadecane*-1 : 10-*bis*(*trimethylammonium iodide*), constant m. p. 198—199° (5·1 g., 95%) (Found : C, 30·5; H, 6·4; I, 45·8. $C_{14}H_{34}N_2S_2I_2$ requires C, 30·7; H, 6·3; I, 46·3%).

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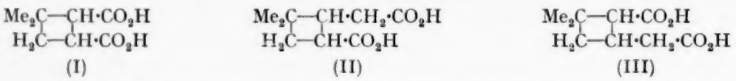
## 596. *The Synthesis of Caryophyllenic Acid.*

By A. CAMPBELL and H. N. RYDON.

4-Carboxy-2 : 2-dimethyl*cyclo*butylacetic acid (II) has been synthesised, separated into *cis*- and *trans*-forms, and resolved. The synthetic *trans*-(+)-acid is identical with *trans*-caryophyllenic acid, prepared from caryophyllene, the structure of which is thus finally established, as also is the orientation of the dimethyl*cyclo*butane ring of caryophyllene with respect to the second ring.

2-Carboxy*cyclo*butylacetic acid has also been synthesised, separated into *cis*- and *trans*-forms, and resolved.

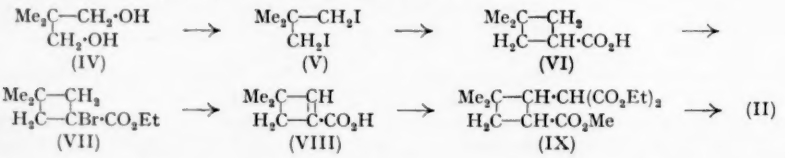
THE synthesis and resolution of norcaryophyllenic acid (I) (Rydon, *J.*, 1936, 593; 1937, 1340) established the presence of a *gem*-dimethyl*cyclo*butane ring in β-caryophyllene but left uncertain the orientation of this ring with respect to the second, larger ring in the sesquiterpene. The final solution of this problem clearly required a synthesis of the higher homologue, caryophyllenic acid, which accompanies norcaryophyllenic acid in the oxidation products of β-caryophyllene (Evans, Ramage, and Simonsen, *J.*, 1934, 1806; Ruzicka and Zimmermann, *Helv. Chim. Acta*, 1935, **18**, 219). The work now reported, which was started in 1947 (cf. Campbell and Rydon, *Chem. and Ind.*, 1951, 312), had as its objective the synthesis of 4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acid (II), which is one of the possible structures for caryophyllenic acid, the other being 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid (III) (Ruzicka, *Chem. and Ind.*, 1935, **54**, 509; Ramage and Simonsen, *J.*,



(I) (II) (III)

1935, 532). During the course of our work, (III) was synthesised and resolved by Dawson and Ramage (*J.*, 1950, 3523) and shown to differ from caryophyllenic acid, while strong degradative evidence for preferring structure (II) to structure (III) was advanced by Barton (*J. Org. Chem.*, 1950, **16**, 457) and by Eschenmoser and Fürst (*Experientia*, 1951, **7**, 290).

Our synthesis was carried out by the following route :



A similar synthesis was attempted by Owen, Ramage, and Simonsen (*J.*, 1938, 1211) but was taken only as far as the bromo-ester (VII). Like these authors, we had difficulty in preparing pure 2 : 2-dimethylpropane-1 : 3-diol (IV) from formaldehyde and *iso*butyraldehyde (Wessely, *Monatsh.*, 1900, **21**, 216, 232; Franke, *ibid.*, 1913, **34**, 1904; Bincer and Hess, *Ber.*, 1928, **61**, 541); a modified method, which gives consistent yields and was used in most of our work, is described in the Experimental section, but the most satisfactory

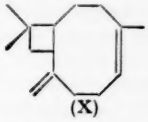
procedure is undoubtedly the lithium aluminium hydride reduction of ethyl dimethylmalonate. The glycol (IV) was converted into the di-iodide (V) in good yield by heating it with triphenyl phosphite and methyl iodide (cf. Landauer and Rydon, *J.*, 1953, 2224); this reaction contributed much to the success of our synthesis since, not only is this preparation much more convenient than that of the dibromide (Gustavson and Popper, *J. pr. Chem.*, 1898, **58**, 458; Owen, Ramage, and Simonsen, *loc. cit.*), but the di-iodide is more reactive than the dibromide and gives a very satisfactory yield of 3 : 3-dimethyl*cyclo*butanecarboxylic acid (VI) by condensation with ethyl malonate, followed by hydrolysis and decarboxylation.

The bromo-ester (VII) was readily obtained from the acid (VI) by the usual Hell–Volhard–Zelinsky procedure but its dehydrobromination was a matter of great difficulty; more conventional methods failing, this was finally brought about, in excellent yield, by treatment with potassium hydroxide under vigorously refluxing toluene. Diazomethane esterification of the resulting unsaturated acid (VIII), followed by a Michael reaction with ethyl malonate (ethyl cyanoacetate was unsatisfactory) yielded the tricarboxylic ester (IX) which, on hydrolysis and decarboxylation, gave a mixture of geometrical isomerides of the derived acid (II). This was converted into *trans*-(±)-4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acid, m. p. 81—82°, by hydrochloric acid at 180°; the *cis*-(±)-acid, m. p. 120°, was obtained from the *trans*-acid by heating it with acetic anhydride at 220° and hydrolysing the resulting anhydride.

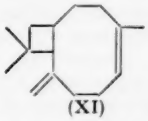
Structural identity of our synthetic *trans*-(±)-acid with *trans*-(+)-caryophyllenic acid prepared from caryophyllene was established by the identity of their infra-red absorption spectra in carbon disulphide solution. Although this evidence is conclusive, comparison of optically active and optically inactive substances in this way has rarely, if ever, been used to establish identity, and it seemed desirable to confirm the conclusion by a more conventional method.

The usual type of base (quinine, brucine, strychnine, morphine, cinchonine, cinchonidine, 2-amino-1-*p*-nitrophenylpropane-1 : 3-diol) having failed, the synthetic *trans*-(±)-acid was successfully resolved with the aid of quinine methohydroxide (Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368). The (+)- and (−)-*trans*-4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acids so obtained had m. p. 81—82° and $[\alpha]_D^{20}$ +28·5° and −28·0°, respectively. Both acids crystallised from *cyclo*hexane in needles similar in appearance to *trans*-(+)-caryophyllenic acid, m. p. 81—82°, $[\alpha]_D^{20}$ +28·0°, prepared from caryophyllene; a mixture of the naturally derived and the synthetic acid melted at 81—82°. The identity was further confirmed by converting the synthetic *trans*-acids and that from caryophyllene into the *cis*-isomerides by the usual acetic anhydride procedure; the synthetic *cis*-(+)- and *cis*-(−)-acids [obtained from the *trans*-(−)- and *trans*-(+)-acids, respectively], had m. p. 77—78° and $[\alpha]_D^{20}$ +41·0° and −41·0°, while the *cis*-(−)-acid from caryophyllene had m. p. 77—78° and $[\alpha]_D^{20}$ −43°; a mixture of the last-named acid with the synthetic *cis*-(−)-acid melted at 77—78°. The identity of the synthetic acids with those from caryophyllene is thus completely established and it follows that caryophyllenic acid has the structure (II).

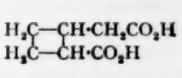
This proof of the structure of caryophyllenic acid establishes beyond doubt the orientation of the dimethyl*cyclo*butane ring in caryophyllene with respect to the nearest oxidisable centres in the larger ring; in terms of the currently accepted structure of β-caryophyllene (Dawson, Ramage, and Wilson, *Chem. and Ind.*, 1951, 464; Barton, Bruun, and Lindsay, *J.*, 1952, 2210), it follows from our work that, of the two alternative possibilities, (X) and (XI), the former is correct.



(X)



(XI)



(XII)

Our synthesis of caryophyllenic acid was guided by model experiments on the synthesis of 2-carboxy*cyclo*butylacetic acid (XII) from the readily accessible *cyclo*butanecarboxylic acid (Cason and Allen, *J. Org. Chem.*, 1949, **14**, 1036), which was carried out by a similar

series of reactions described in the Experimental section. The only noteworthy point which arises from this part of our work is the great difference in stability between *cyclo*but-1-enecarboxylic acid and the 3 : 3-dimethyl compound, the former absorbing oxygen so rapidly from the air as to make it almost impossible to obtain a satisfactory analysis for carbon and hydrogen. All six stereoisomerides of 2-carboxy*cyclo*butylacetic acid were obtained (see Table):

| | *trans* | | | *cis* | | |
|---|---|---|---|---|---|---|
| Acid | (±) | (+) | (−) | (±) | (+) | (−) |
| M. p. ..... | 64·5° | Oil | Oil | 110—111° | 110—111° | 110—111° |
| $[\alpha]_D^{20}$ ..... | — | +73° | −71° | — | +43° | −45° |

In this series, as with the caryophyllenic acids, geometrical inversion was accompanied by inversion of the sign of rotation. The low melting point of the *trans*-acid, compared with the *cis*-, is an exception to the usually accepted relationship and is paralleled by the only two other fully investigated cases of carboxy*cyclo*butyl acetic acids (caryophyllenic acid, this paper; 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid, Dawson and Ramage, *loc. cit.*) and by the inactive 2-carboxy*cyclo*pentylacetic acids (Linstead and Meade, *J.*, 1934, 935; Cook and Linstead, *J.*, 1934, 956); it is clear that melting points are a most unreliable guide to configuration.

## Experimental

*Synthesis of (±)-Caryophyllenic Acid.*—*2 : 2-Dimethylpropane-1 : 3-diol* (IV). (*a*) The bulk of the material used in the present work was prepared by the following modification of Franke's method (*Monatsh.*, 1913, **34**, 1904).

*iso*Butyraldehyde (50 g.), dissolved in aqueous formaldehyde (35% w/w; 119 g.) and ethanol (25 ml.), was slowly added to a stirred solution of potassium hydroxide (39 g.) in ethanol (290 ml.), cooled to 0° during, and for 1 hr. after, the addition. The golden-yellow solution was set aside for 12 hr. at room temp. (the time is critical) and then neutralised (phenolphthalein) with acetic acid. Removal of the alcohol under reduced pressure, followed by extraction with ether (15 × 100 ml.), yielded the crude glycol (65 g.), which could only be recrystallised with difficulty and was therefore converted into the diacetate by 6 hours' refluxing with acetic anhydride (104 g.), containing fused sodium acetate (2 g.) and pyridine (2 g.). After removal of acetic acid and excess of acetic anhydride by distillation, the residual ester was dissolved in ether (100 ml.) and washed with 5% sodium hydrogen carbonate solution until neutral. Distillation gave 1 : 3-diacetoxy-2 : 2-dimethylpropane (55 g., 42%; average for 8 runs, 44%), b. p. 105—108°/15 mm., $n_D^{20}$ 1·4348.

This ester (56 g.) was refluxed for 1 hr. with 10% alcoholic potassium hydroxide (400 ml.); removal of alcohol under reduced pressure, followed by exhaustive ether-extraction, drying, evaporation, and crystallisation from benzene, afforded 2 : 2-dimethylpropane-1 : 3-diol (27 g., 37%) as large needles, m. p. 126—127° (lit., m. p. 127°).

(*b*) The glycol can also be prepared by reduction of ethyl dimethylmalonate. Ethyl dimethylmalonate (18·8 g.) was added, under reflux, with stirring, to a solution of lithium aluminium hydride (3·8 g.) in anhydrous ether (100 ml.) at such a rate as to maintain gentle refluxing. Ten min. after completion of the addition water (5 ml.) was added and the mixture then poured into 10% sulphuric acid (50 ml.). Working up as in (*a*) gave the diol (8 g., 82%), m. p. 127°.

1 : 3-*Di-iodo*-2 : 2-*dimethylpropane* (V). The glycol (IV) (10 g.), triphenyl phosphite (68 g.), and methyl iodide (42 g.) were heated together under reflux in an oil-bath at 130° for 24 hr.; the internal temperature rose from 68° to 130° during the reaction; occasionally a little methyl iodide had to be distilled off at this stage to raise the internal temperature to 130°. Heating was then continued at 130° for a further 36 hr.; at lower temperatures the reaction is incomplete, whereas higher temperatures cause serious decomposition. After cooling, the product was dissolved in ether (200 ml.), washed with 5% sodium hydroxide solution, dried ($K_2CO_3$), and twice distilled, yielding 1 : 3-*di-iodo*-2 : 2-*dimethylpropane* (24 g., 75%; average for 6 runs, 76%), b. p. 70—71°/0·1 mm., $n_D^{20}$ 1·5938 (Found: I, 78·6. $C_5H_{10}I_2$ requires I, 78·4%).

3 : 3-*Dimethyl*cyclo*butanecarboxylic acid* (VI). Ethyl malonate (45 g.), followed by 1 : 3-di-iodo-2 : 2-dimethylpropane (90 g.), was added to a solution of potassium *iso*butoxide prepared from potassium (22 g.) and anhydrous *iso*butyl alcohol (600 ml.), and the mixture refluxed, with stirring, for 100 hr. Potassium hydroxide (40 g.) in 50% v/v aqueous ethanol (200 ml.)

was then added and refluxing continued for a further 8 hr. *iso*Butyl alcohol was then removed by steam-distillation and the residual solution acidified with hydrochloric acid and extracted with ether. Evaporation of the dried extract gave crude **3 : 3-dimethyl*cyclo*butane-1 : 1-dicarboxylic acid** (38 g.) [a specimen crystallised from ethyl acetate in stout needles, m. p. 162° (decomp.), in agreement with Owen, Ramage, and Simonsen, *loc. cit.*], which was decarboxylated at 180° for 1 hr. and then distilled, yielding **3 : 3-dimethyl*cyclo*butanecarboxylic acid** (27 g., 73%; average for 4 runs, 61%), b. p. 105—106°/15 mm., $n_D^{20}$ 1·4317, characterised as the p-*bromophenacyl* ester, plates (from ethanol), m. p. 93° (Found: C, 55·7; H, 5·3; Br, 24·5. $C_{15}H_{17}O_3Br$ requires C, 55·4; H, 5·2; Br, 24·6%). Substitution of *tert.*-butyl alcohol for *iso*butyl alcohol reduced the yield to 11%.

*Ethyl* **1-*bromo*-3 : 3-*dimethyl*cyclo*butanecarboxylate*** (VII). The acid (VI) (90 g.) was heated under reflux at 100° for 1 hr. with purified thionyl chloride (90 g.). Red phosphorus (1 g.) and bromine (120 g.; dried under concentrated sulphuric acid) were then added and heating continued at 110—120° for a further 3 hr. The cooled product was poured into absolute ethanol (100 ml.), diluted with water (200 ml.), and extracted with ether. Distillation of the dried extract gave ***ethyl* 1-*bromo*-3 : 3-*dimethyl*cyclo*butanecarboxylate*** (114 g., 69%), b. p. 46—47°/0·7 mm., $n_D^{20}$ 1·4550 (Found: C, 46·1; H, 6·7; Br, 32·2. $C_9H_{15}O_2Br$ requires C, 45·9; H, 6·4; Br, 34·0%).

**3 : 3-*Dimethyl*cyclo*but*-1-*enecarboxylic acid*** (VIII). Molten potassium hydroxide (10 g.) was stirred vigorously under refluxing toluene (150 ml.) while ethyl 1-bromo-3 : 3-dimethyl-*cyclo*butanecarboxylate (10 g.) was added dropwise; a vigorous exothermic reaction set in and the source of heat was removed during the addition; solid potassium salts separated. After completion of the addition, heating was resumed for a further 40 min. and the mixture was then cooled before addition of water (100 ml.). The aqueous solution was separated, washed with light petroleum (b. p. 40—60°) (50 ml.), acidified with 30% w/w sulphuric acid and extracted with ether (4 × 50 ml.); evaporation of the dried extract gave the crude acid as a viscous yellow oil (5·2 g., 97%) which crystallised. Distillation gave **3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylic acid***, b. p. 76—77°/1 mm., which crystallised from light petroleum (b. p. 40—60°) at −30° in plates, m. p. 54—55° [Found: C, 66·4; H, 7·8%; Equiv. (by titration), 126. $C_7H_{10}O_2$ requires C, 66·7; H, 7·9%; Equiv., 126]. Addition of bromine in carbon tetrachloride, followed by evaporation and crystallisation from light petroleum (b. p. 40—60°), afforded **1 : 2-*dibromo*-3 : 3-*dimethyl*cyclo*butanecarboxylic acid*** in prisms, m. p. 88—89° [Found: C, 29·2; H, 3·2%; Equiv. (by titration), 284. $C_7H_{10}O_2Br_2$ requires C, 29·4; H, 3·5%; Equiv., 286].

***Methyl* 3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylate***. The crude acid (VIII) (5·2 g.) was added to a solution of diazomethane (1·8 g.) in ether (50 ml.). Distillation through a short column packed with Fenske helices gave ***methyl* 3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylate*** (4·8 g., 82%) as a mobile liquid with a penetrating pineapple odour, b. p. 52°/14 mm., $n_D^{20}$ 1·4360 (Found: C, 68·7; H, 8·7. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%).

Distillation of the combined residues from several preparations gave methyl 1-hydroxy-3 : 3-dimethyl*cyclo*butanecarboxylate, b. p. 68—70°/7 mm., $n_D^{20}$ 1·4185, identified by hydrolysis to the acid, m. p. and mixed m. p. 83°.

*Ethyl* **(4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)*malonate*** (IX). Methyl **3 : 3-dimethyl*cyclo*but-1-enecarboxylate** (4·8 g.) was added to a solution of ethyl potassiomalonate, prepared from potassium (0·5 g.), anhydrous *tert.*-butyl alochol (25 ml.), and ethyl malonate (5 g.), and the mixture refluxed for 2 hr. After addition of acetic acid (1 ml.), the mixture was cooled and dissolved in ether (100 ml.). After being washed with 5% w/w sodium hydrogen carbonate solution until neutral and dried ($Na_2SO_4$), the product was distilled, yielding ***ethyl* (4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)*malonate*** (6 g., 58%; average in 4 runs, 57%), b. p. 103°/0·1 mm., $n_D^{20}$ 1·4492 (Found: C, 59·8; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·0%).

A similar preparation, using ethyl cyanoacetate (4 g.) in place of ethyl malonate, yielded ***ethyl* α-(4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)-α-*cyanoacetate*** (0·75 g., 8·6%), b. p. 144—145°/0·5 mm., $n_D^{20}$ 1·4626 (Found: C, 61·6; H, 7·4; N, 5·7. $C_{13}H_{19}O_4N$ requires C, 61·7; H, 7·5; N, 5·5%); the yield was not improved by varying the proportion of the reactants or by longer heating.

***(±)-Caryophyllenic acids***. Ethyl (4-carbomethoxy-2 : 2-dimethyl*cyclobutyl*)*malonate* (25 g.) was heated under reflux with constant-boiling hydrochloric acid (50 ml.) for 20 hr. Dilution with an equal volume of water, followed by extraction with ether (10 × 100 ml.), drying, and evaporation, yielded a mixture of the *cis*- and the *trans*-(±)-acid (14·5 g., 93·5%) as an oil which slowly crystallised in a vacuum-desiccator. This mixture (14 g.) was heated with concentrated hydrochloric acid (50 ml.) in a sealed tube at 180° for 5 hr. The solution, diluted with two volumes

of water, was extracted with light petroleum (b. p. 40—60°; 2 × 100 ml.), to remove a dark, oily decomposition product (5 g.), and then boiled with decolorising charcoal, filtered, and evaporated to dryness under reduced pressure. The crude *trans*-(±)-acid so obtained (7·5 g., 53%) was neutralised with a solution of potassium hydroxide (5·5 g.) in absolute methanol (25 ml.); after 1 hr. at 0° the insoluble potassium salt was filtered off and dissolved in water; acidification, followed by extraction with ether (10 × 100 ml.), evaporation of the dried extract, and crystallisation from *cyclo*hexane yielded trans-(±)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*trans*-(±)-caryophyllenic acid] (II) as rosettes of short, curved needles, m. p. 81—82° [Found : C, 58·5; H, 7·7%; Equiv. (by titration), 93. $C_9H_{14}O_4$ requires C, 58·0; H, 7·5%; Equiv., 93]. The infra-red absorption spectrum of a carbon disulphide solution of this compound in the 1350—1900- and 850—665-cm.$^{-1}$ regions was kindly determined by Mr. S. F. D. Orr, of the Chester Beatty Research Institute, Royal Cancer Hospital, who found it indistinguishable from that of authentic *trans*-(+)-caryophyllenic acid prepared from caryophyllene.

The *trans*-(±)-acid (0·5 g.) was heated with acetic anhydride (5 ml.) in a sealed tube at 220° for 6 hr. Distillation gave the *cis*-anhydride as an oil, b. p. 110—112°/0·5 mm. Digestion with water, followed by crystallisation from *cyclo*hexane, in which the acid is difficultly soluble, yielded cis-(±)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*cis*-(±)-carophyllenic acid] in small prisms, m. p. 120° [Found : C, 58·2; H, 7·7%; Equiv. (by titration), 93].

*Resolution of Caryophyllenic Acid.*—Quinine methohydroxide solution (0·41N; 79 ml.) (Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368) was exactly neutralised by the addition of *trans*-(±)-caryophyllenic acid (3 g.). The salt (16·9 g.), obtained by evaporating the solution to dryness, was dissolved in absolute ethanol (15 ml.) and the solution diluted with pure dioxan (150 ml.). The salt which crystallised out in small balls of fine needles (9·5 g.), $[\alpha]_D^{20}$ −134° (*c* = 1·121 in EtOH) was thrice recrystallised similarly, giving the pure quinine metho-salt of *trans*-(−)-caryophyllenic acid in rosettes of fine needles (3·5 g.), m. p. 202—203°, $[\alpha]_D^{20}$ −148° (*c* = 1·421 in EtOH). This salt was dissolved in 10% w/w sulphuric acid, and the organic acid removed by extraction with ether (10 × 100 ml.) as a yellow oil, which rapidly crystallised. Purification through the sparingly soluble potassium salt, followed by crystallisation from *cyclo*hexane, yielded trans-(−)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*trans*-(−)-caryophyllenic acid] as rosettes of long needles, m. p. 81—82°, $[\alpha]_D^{20}$ −28° (*c* = 2·125 in $C_6H_6$) (Found : C, 58·3; H, 7·3%; Equiv. (by titration), 93].

Recovery of the acid from the more soluble metho-salt of the *cis*-acid, contained in the filtrate from the original crude *trans*-salt, gave an oil (2·3 g.) which, on fractional crystallisation from *cyclo*hexane, yielded pure trans-(+)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*trans*-(+)-caryophyllenic acid] (0·15 g.) as long needles, m. p. 81—82°, $[\alpha]_D^{20}$ +28·5° (*c* = 1·452 in $C_6H_6$) [Found : C, 57·9; H, 7·4%; Equiv. (by titration), 93]. A 50% mixture of this acid with authentic *trans*-(+)-caryophyllenic acid, m. p. 81—82°, $[\alpha]_D^{20}$ +28° (*c* = 1·468 in $C_6H_6$), prepared from caryophyllene essentially by the method of Evans, Ramage, and Simonsen (*J.*, 1934, 1807), but omitting the preliminary permanganate oxidation, melted at 81—82°.

Synthetic *trans*-(+)-caryophyllenic acid (300 mg.) was heated with acetic anhydride (3 ml.) in a sealed tube at 220° for 6 hr. Distillation yielded the *cis*-anhydride (180 mg.), b. p. 110—111°/0·5 mm., which, on digestion with water, gave the *cis*-(−)-acid (190 mg.). Two crystallisations from *cyclo*hexane yielded pure cis-(−)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*cis*-(−)-caryophyllenic acid] as long needles, m. p. 77—78°, $[\alpha]_D^{20}$ −42° (*c* = 1·314 in $C_6H_6$) [Found : C, 57·9; H, 7·4%; Equiv. (by titration), 93]. A 50% mixture of this acid with authentic *cis*-(−)-caryophyllenic acid, m. p. 77—78°, $[\alpha]_D^{20}$ −43° (*c* = 2·421 in $C_6H_6$), from caryophyllene, melted at 77—78°.

Similar treatment of synthetic *trans*-(−)-caryophyllenic acid yielded cis-(+)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* in long silky needles, m. p. 77—78°, $[\alpha]_D^{20}$ +41° (*c* = 1·482 in $C_6H_6$) [Found : C, 58·3; H, 7·2%; Equiv. (by titration), 93].

*Synthesis and Resolution of* 2-*Carboxy*cyclo*butylacetic Acid.*—cyclo*But*-1-*enecarboxylic acid. cyclo*Butanecarboxylic acid (50 g.) (Cason and Allen, *J. Org. Chem.*, 1949, **14**, 1036) and pure thionyl chloride (65·5 g.) were heated under reflux at 110° for 1 hr., and then with red phosphorus (0·5 g.), bromine (88 g.), and later ethanol, etc., as in the preparation of (VII), gave ethyl 1-bromo-*cyclo*butanecarboxylate (61·5 g., 77·5%; average for 8 runs, 71%), b. p. 67—68°/5 mm., $n_D^{20}$ 1·4691.

This bromo-ester (20 g.) was treated with potassium hydroxide (20 g.) in toluene (250 ml.) as in the previous case and worked up similarly. The aqueous layer was extracted once with light petroleum (b. p. 40—60°; 100 ml.), acidified with 30% w/w sulphuric acid and extracted with ether (5 × 50 ml.). Quinol (200 mg.) was added to the dried extract, from which the ether

was then removed under reduced pressure. The partly crystalline residue was warmed to 40° with light petroleum (b. p. 40—60°; 80 ml.), and the extract decanted and cooled to −20°; the needles which separated were filtered off and stored at 0°. This extraction process was repeated until no more crystals were obtained; the total yield of crystalline acid was 6·8 g. (72%). One recrystallisation from light petroleum (b. p. 40—60°) at −20° yielded cyclo*but*-1-*enecarboxylic acid* in needles, m. p. 72° [Found: Equiv. (by titration), 98. $C_5H_6O_2$ requires Equiv., 98]. A satisfactory analysis for carbon and hydrogen could not be obtained owing to rapid polymerisation and absorption of atmospheric oxygen (Found, 12 hr. after preparation: C, 60·2; H, 6·0. 36 hr. after preparation: C, 58·1; H, 5·9. Calc. for $C_5H_6O_2$: C, 61·2; H, 6·1%).

cis- *and* trans-(±)-2-*Carboxy*cyclo*butylacetic acids*. Freshly prepared *cyclo*but-1-enecarboxylic acid (6 g.) in ether (25 ml.) containing quinol (200 mg.) was treated at 0° with an excess of ethereal diazomethane. Distillation gave methyl *cyclo*but-1-enecarboxylate (6·8 g., 87·5%) as a mobile liquid, with a penetrating pineapple-like odour, b. p. 42—43°/25 mm., $n_D^{20}$ 1·4492, which rapidly polymerised to a hard resin.

This ester (6·8 g.) was added, with shaking, to a solution of ethyl potassiomalonate (from potassium 0·5 g., *tert.*-butyl alcohol 150 ml., and ethyl malonate 15 g.) at 10°. After 3 hr. at room temperature, glacial acetic acid (1 ml.) was added and the mixture diluted with water (100 ml.) and extracted with ether (2 × 100 ml.). Distillation gave *ethyl* (2-*carbomethoxy*-cyclo*butyl*)*malonate* (5·6 g., 54%), b. p. 105—106°/0·3 mm., $n_D^{20}$ 1·4993 (Found: C, 57·05; H, 7·4. $C_{13}H_{20}O_6$ requires C, 57·4; H, 7·4%). The experimental conditions for this condensation are critical; unsatisfactory results are obtained by increasing the time of standing or the amount of potassium *tert.*-butoxide or by heating the reaction mixture.

Ethyl (2-carbomethoxy*cyclo*butyl)malonate (20 g.) was refluxed for 1 hr. with potassium hydroxide (10 g.) in 50% aqueous ethanol (100 ml.), and the ethanol then removed by distillation. The cooled residue was diluted with an equal volume of water, acidified with 30% w/w sulphuric acid and extracted with ether (20 × 200 ml.). Evaporation of the dried extract left a gum (13·8 g.) which was heated at 180° for 1 hr. One crystallisation from benzene gave crude *cis*-(±)-2-carboxy*cyclo*butylacetic acid in needles, m. p. 110—111° [Found: Equiv. (by titration), 79. $C_7H_{10}O_4$ requires Equiv., 79]. This material (5 g.) was heated with acetic anhydride (20 ml.) to 220° in a sealed tube for 6 hr. Distillation yielded cis-(±)-2-*carboxy*-cyclo*butylacetic anhydride* (4·8 g., 97%) as an oil, b. p. 102—103°/0·5 mm., $n_D^{20}$ 1·4868 (Found: C, 59·9; H, 5·8. $C_7H_8O_3$ requires C, 60·0; H, 5·7%). Digestion of this anhydride with water and evaporation of the resulting solution gave cis-(±)-2-*carboxy*cyclo*butylacetic acid* (4·9 g., 90%) which crystallised from benzene in needles, m. p. 110—111° [Found: C, 53·3; H, 6·5%; Equiv. (by titration), 79. $C_7H_{10}O_4$ requires C, 53·2; H, 6·3%; Equiv., 79].

Alternatively, methyl *cyclo*but-1-enecarboxylate (8·3 g.) was added, with cooling and shaking, to a solution of ethyl potassiocyanoacetate prepared from potassium (2·9 g.), *tert.*-butyl alcohol (100 ml.) and ethyl cyanoacetate (10 g.). After 3 hr. at room temperature, the mixture was acidified with acetic acid (4 g.), diluted with water, and extracted with ether (2 × 100 ml.). Distillation afforded *ethyl* α-(-2-*carbomethoxy*cyclo*butyl*)-α-*cyanoacetate* (7·1 g., 52%) as an oil, b. p. 144—155°/0·1 mm., $n_D^{20}$ 1·4678 (Found: C, 58·6; H, 6·7; N, 6·3. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·6; N, 6·2%). This ester (10 g.) was refluxed for 20 hr. with constant-boiling hydrochloric acid (50 ml.). The resulting dark solution was diluted with an equal volume of water, boiled with charcoal (2 g.), filtered, cooled, and extracted with ether (10 × 100 ml.). Evaporation of the dried extract yielded a brown oil (7 g.) which deposited crystals during 6 weeks in a vacuum-desiccator. The crystals (1 g.) were recrystallised from benzene, affording *cis*-(±)-2-carboxy*cyclo*butylacetic acid, m. p. 110—112° [Found: Equiv. (by titration), 79].

The *cis*-(±)-acid (5 g.) was heated in a sealed tube at 180° for 5 hr. with concentrated hydrochloric acid (20 ml.). Evaporation gave an oil (5 g.) which crystallised when rubbed; two recrystallisations from anhydrous ether–*cyclo*hexane (1 : 10) afforded trans-(±)-2-*carboxy*cyclo-*butylacetic acid* in rhombohedra, m. p. 64—65° [Found: C, 53·1; H, 6·1%; Equiv. (by titration), 78. $C_7H_{10}O_4$ requires C, 53·2; H, 6·3%; Equiv., 79].

*Resolution of* 2-*carboxy*cyclo*butylacetic acid*. Quinine methohydroxide solution (0·39N; 97·4 ml.) (Major and Finkelstein, *loc. cit.*) was exactly neutralised by the addition of the *cis*-(±)-acid (3 g.). The salt, recovered by evaporation under reduced pressure, was dissolved in absolute ethanol (20 ml.) and the resulting solution diluted with pure dioxan (200 ml.). The salt which separated rapidly in fluffy needles (8 g.), m. p. 220—224° (decomp.), $[\alpha]_D^{20}$ −140° ($c$ = 2·105 in EtOH), was recrystallised six times by a similar procedure. The final product (3·5 g.), which had m. p. 225—226°, $[\alpha]_D^{20}$ −154° ($c$ = 1·024 in EtOH), was decomposed with

10% w/w sulphuric acid; extraction with ether (15 × 100 ml.) yielded the crude *cis*-(−)-acid (350 mg.), m. p. 105—106°, $[\alpha]_D^{20}$ −34° (*c* = 1·216 in EtOH). Fractional crystallisation from benzene afforded cis-(−)-2-*carboxy*cyclo*butylacetic acid* (190 mg.) in clusters of long needles, m. p. 110—111°, $[\alpha]_D^{20}$ −45° (*c* = 1·254 in EtOH) [Found: C, 53·1; H, 6·4%; Equiv. (by titration), 79]. Fractional crystallisation of the acid recovered from the more soluble quinine metho-salt yielded cis-(+)-2-*carboxy*cyclo*butylacetic acid* (140 mg.) in rosettes of thin needles, m. p. 110—111°, $[\alpha]_D^{20}$ +43° (*c* = 2·15 in EtOH) [Found: C, 53·3; H, 6·2%; Equiv. (by titration), 79].

The pure *cis*-(+)-acid (500 mg.) was heated in a sealed tube at 180° for 5 hr. with concentrated hydrochloric acid (5 ml.). Evaporation, followed by dissolution in ether, treatment with charcoal (300 mg.), and re-evaporation afforded trans-(−)-2-*carboxy*cyclo*butylacetic acid* as an oil, $[\alpha]_D^{20}$ −71° (*c* = 0·92 in EtOH), which resisted all attempts at crystallisation [Found: C, 52·9; H, 6·1%; Equiv. (by titration), 78]. Similar treatment of the pure *cis*-(−)-acid yielded trans-(+)-2-*carboxy*cyclo*butylacetic acid* as an uncrystallisable oil, $[\alpha]_D^{20}$ +73° (*c* = 0·84 in EtOH) [Found: C, 52·9; H, 6·4%; Equiv. (by titration), 79·5].

We are greatly indebted to Mr. S. F. D. Orr of the Chester Beatty Research Institute, Royal Cancer Hospital, for the infra-red spectra and to Professor L. Ruzicka and Dr. A. Fürst, of the Eidgenössische Technische Hochschule, Zürich, for an authentic specimen of *trans*-(+)-caryophyllenic acid. Analyses of *cyclo*but-1-enecarboxylic acid were carried out at the Organic Chemistry Department, Imperial College of Science and Technology, by Mr. F. H. Oliver.

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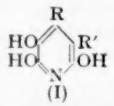
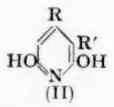
## 597. *Synthesis of Some Methyl-substituted* 2 : 3 : 6-*Trihydroxypyridines.*

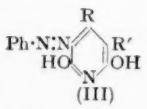
By D. E. AMES, R. E. BOWMAN, and T. F. GREY.

The dihydroxypyridines (II; R = Me, R′ = H or Me) have been converted, *via* the phenylazo- (III) and diacetylamino-compounds (IV), into the corresponding trihydroxypyridines (I). Methylation of (II) with diazomethane has been investigated, various *O*- and *N*-methyl derivatives being isolated. The infra-red and ultra-violet spectra of these products are discussed.

Two of the six possible trihydroxypyridines have been known for many years but, as far as we are aware, none of the remaining isomers or any corresponding nuclear-alkylated compounds have been described. 2 : 3 : 4-Trihydroxypyridine and analogous alkyl derivatives have been prepared by Ost (*J. pr. Chem.*, 1883, **27**, 257), Lapworth and Collie (*J.*, 1897, **71**, 838) and others; the other known isomer is the 2 : 4 : 6-compound (*inter al.*, Baron, Remfry, and Thorpe, *J.*, 1904, **85**, 1742; Schroeter, Seidler, Sulzbacher, and Kanitz, *Ber.*, 1932, **65**, 432; and Jacini, *Gazzetta*, 1938, **68**, 592). The two methyl-substituted trihydroxypyridines (I; R = Me, R′ = H or Me) have now been synthesised for examination as possible antibacterial agents.


(I)

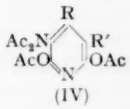

(II)

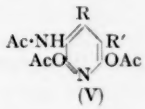

(III)

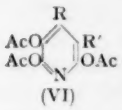
The dihydroxy-base (II; R = Me, R′ = H), prepared from ethyl α-cyano-β-methylglutaconate essentially by the method of Rogerson and Thorpe (*J.*, 1905, **87**, 1685), was coupled with benzenediazonium chloride to give the azo-compound (III; R = Me, R′ = H). Reduction of the latter with zinc–acetic acid–acetic anhydride, followed by prolonged boiling of the insoluble products with acetic anhydride, furnished

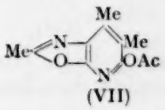
the tetra-acetyl derivative (IV; R = Me, R′ = H); when acetylation was incomplete the triacetyl compound (V; R = Me, R′ = H) could be isolated, though only in poor yield.

When (IV) was hydrolysed with hydrochloric acid, the β-amino-group was replaced by hydroxyl; similar displacement of the β-amino-group in a related dihydroxypyridine derivative was described by Lapworth and Collie (*loc. cit.*). Separation of the rather unstable, amphoteric trihydroxy-base from the ammonium chloride also formed proved


(IV)

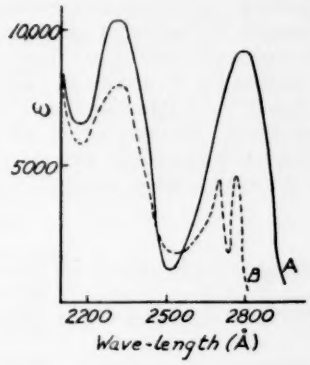

(V)


(VI)


(VII)

difficult and the product was therefore converted into the triacetate (VI; R = Me, R′ = H) which was purified by distillation. Hydrolysis with hydrochloric acid then gave the hydrochloride of (I; R = Me, R′ = H), the hydroxy-base itself being obtained by reaction with one equivalent of diazomethane. This method was used as the compound was susceptible to autoxidation in alkaline solution.

The synthesis of (I; R = R′ = Me) was effected similarly. Acetyl compounds of



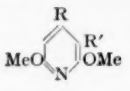

*A*, 6-*Acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine*.
*B*, 2-*Methylbenzoxazole*.

types (IV) and (V) were obtained in this case also and were similarly converted into the hydrochloride (I; R = R′ = Me).

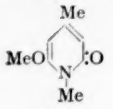
During preliminary experiments on the reductive acetylation of (III), non-crystalline products were encountered, probably owing to incomplete acetylation. When one of these mixtures (from III; R = R′ = Me) or the triacetyl derivative (V; R = R′ = Me) was distilled, a crystalline substance, $C_{11}H_{12}O_3N_2$, m. p. 119—120°, was obtained which gave two mols. of acetic acid on hydrolysis and contained no active hydrogen (Zerewitinov). The infra-red spectrum showed that amide and hydroxyl groups were absent but bands at 1748 (ester C=O) and 1193 cm.$^{-1}$ (C–O) showed the presence of one or more acetoxy-groups. This evidence, together with the mode of formation, suggests that this material is 6-acetoxy-4 : 5 : 2′-trimethyloxazolo(5′ : 4′-2 : 3)pyridine (VII). The ultra-violet absorption curves of this material and of 2-methylbenzoxazole are similar (see Fig.), and the chief differences are in accord with the observations by Badger, Pearce, and Pettit (*J.*, 1951, 3199) that replacement of CH by N in aromatic systems causes a considerable loss of fine structure and increases the intensity of absorption bands at longer wave-lengths. It is shown below that the presence of the methyl and acetoxy-groups in the pyridine ring causes only slight change in the spectrum.

Methylation of the dihydroxypyridines of type (II) was also investigated. Diazomethane and (II; R = Me, R′ = H) gave a mixture from which three products were isolated. The first, m. p. 33—33·5°, was evidently the dimethoxy-compound (VIII; R = Me, R′ = H) as it could be separated by distillation whereas the other two compounds

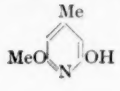
were much less volatile. A second dimethylation product, m. p. 92°, isolated by fractional crystallisation, must be 6-methoxy-1 : 4-dimethylpyrid-2-one (IX). The third substance was a monomethylation product, presumably (X*a*) or the tautomeric form (X*b*),



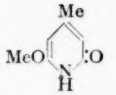
(VIII)



(IX)

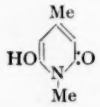


(X*a*)

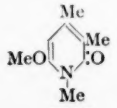


(X*b*)

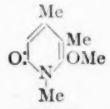
or possibly (XI). The structures assigned to these three compounds accord with the spectroscopic data (see below).



(XI)



(XII)



(XIII)

In the case of (II; R = R′ = Me), no monomethylation product was isolated after treatment with diazomethane; a dimethoxy-compound and an isomer, m. p. 119—120°, were obtained, however, and, in one experiment, a third dimethylation product, m. p. 85—87°. The two isomers had infra-red spectra similar to that of (IX) and they are evidently the two possible methoxy-1-methylpyridones (XII and XIII). Since steric effects would be expected to lead to the formation of (XII) rather than (XIII), the compounds, m. p. 119—120° and 85—87°, are formulated as (XII) and (XIII) respectively, the yield of the latter being very small. Methylation of (II; R = R′ = Me) with methyl sulphate also furnished the dimethoxy-compound and the product, m. p. 119—120°.

Comparison of the ultra-violet absorption spectra (see Table) of the series derived from

| | Ethanol | | 0·1N-HCl | | Alkali (pH 8·9) | |
|---|---|---|---|---|---|---|
| | $\lambda_{max.}$ (Å) | ε | $\lambda_{max.}$ (Å) | ε | $\lambda_{max.}$ (Å) | ε |
| (II; R = Me, R′ = H) | 2400 | 7,600 | 2085 | 7,600 | 2375 | 8,000 |
| | 3220 | 13,100 | 2910 | 6,900 | 3170 | 14,600 |
| (II; R = R′ = Me) | 2380 | 6,400 | 2100 * | 9,900 | 2370 | 7,700 |
| | 3230 | 7,800 | 2510 | 3,900 | 3250 | 14,800 |
| | | | 2970 | 4,000 | | |
| (I; R = Me, R′ = H) | 2505 | 9,400 | 2530 | 9,900 | — | — |
| (I; R = R′ = Me) | — | — | 2550 | 11,900 | — | — |
| | | | 3050 | 1,800 | | |
| (VIII; R = Me, R′ = H) | 2270 | 7,400 | 2140 | 3,300 | 2215 | 5,100 |
| | 2765 | 6,600 | 2890 | 11,500 | 2760 | 6,800 |
| (VIII; R = R′ = Me) | 2275 | 8,200 | 2230 | 4,700 | 2230 | 6,500 |
| | 2810 | 7,100 | 2920 | 7,800 | 2805 | 7,000 |
| 2 : 6-Diacetoxy-4-methylpyridine | 2600 | 3,600 | 2590 | 3,700 | — | — |
| 2 : 6-Diacetoxy-3 : 4-dimethylpyridine | 2630 | 4,200 | 2625 | 4,100 | — | — |
| 2 : 5 : 6-Triacetoxy-4-methylpyridine | 2630 | 3,900 | 2625 | 3,800 | — | — |
| | 3290 | 450 | | | | |
| 2 : 5 : 6-Triacetoxy-3 : 4-dimethylpyridine | 2665 | 4,700 | — | — | — | — |
| (IV; R = Me, R′ = H) | 2640 | 3,900 | 2630 | 4,000 | — | — |
| (IV; R = R′ = Me) | 2675 | 3,800 | 2675 | 3,900 | — | — |
| (IX) | 2320 | 5,600 | — | — | — | — |
| | 3035 | 9,100 | | | | |
| (X) or (XI) | 2280 | 6,400 | — | — | — | — |
| | 2880 | 5,400 | | | | |
| | 3020 | 6,800 | | | | |
| (XII) | 2330 | 4,900 | 2310 | 3,700 | 2310 | 4,500 |
| | 3070 | 9,500 | 3050 | 9,900 | 3060 | 10,000 |
| 1-Methylpyrid-2-one † | 2300 | 6,000 | — | — | — | — |
| | 3050 | 5,000 | | | | |

* Inflection. † Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2092.

(II) and (I) shows that introduction of the second methyl group causes a slight bathochromic shift, usually of 30—50 Å, as with toluene and *o*-xylene (Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414).

The spectra of the acetylation products of (I) and (II) are similar to those of pyridine and the picolines (Daeniker, *Helv. Chim. Acta*, 1952, **35**, 1955); replacement of a hydrogen atom by an acetoxy-group in an aromatic system usually results in only a slight change in the spectrum (see, *e.g.*, Braude, *J.*, 1949, 1906). Closely similar spectra are also shown by the tetra-acetyl derivatives in accordance with the assigned structures (IV); the facility with which the amino-group is diacetylated is rather surprising in view of the highly substituted ring system present. The formation of diacetyl derivatives of various substituted 3-aminopyridines has been reported by Schickh, Binz, and Schulz (*Ber.*, 1936, **69**, 2593), Clemo and Swan (*J.*, 1948, 198), and den Hertog, Kolder, and Combé (*Rec. Trav. chim.*, 1951, **70**, 591). Structures (V) appear to be probable for the corresponding triacetyl compounds but the absorption spectra are complicated by interaction with the solvent (ethanol). This instability seems difficult to explain in comparison with the relatively stable nature of the tetra-acetyl compounds; alternative structures, such as 1-acylpyridones appear to be unlikely, however, because conversion into (IV) can be effected by boiling acetic anhydride. Furthermore, the infra-red spectra provide evidence favouring the structures (V): first, a strong band in the range 1600—1613 cm.$^{-1}$ indicates the presence of a true pyridine ring (see below); and, secondly, intense bands at about 3270 (N–H), 1650 and 1520 cm.$^{-1}$ are characteristic of an amide group.

The dimethoxypyridines (VIII) show the expected ultra-violet light absorption properties (cf. den Hertog, Wibaut, Schepman, and van der Wal, *Rec. Trav. chim.*, 1950, **69**, 700). Since aromatic methoxy- and hydroxy-compounds generally possess very similar absorption spectra (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127; Burawoy and Chamberlain, *J.*, 1952, 2310), the great differences in the case of (II) and (VIII) must indicate that the former exist largely in hydroxypyridone forms as in the case of pyrid-2-one (cf. Mosher, "Heterocyclic Compounds," Vol. I, Ed. Elderfield, Wiley, 1950, p. 436). The spectra of the other methylation products are almost identical with that of 1-methylpyrid-2-one (see Table) in accordance with the assigned structures. This evidence indicates that the monomethylation product exists as (X*b*) rather than (X*a*), though the alternative structure (XI) cannot be excluded.

In contrast with those of dihydroxypyridines, the spectra of the trihydroxypyridines (I) are almost the same in ethanol and in dilute acid (oxidative decomposition occurred in alkaline solution), a situation which may be due to the formation of a zwitterion in both media.

All the compounds of the diacetoxy-, triacetoxy-, and dimethoxy-pyridine series already described and those of types (IV) and (V) show an intense infra-red absorption band in the range 1600—1613 cm.$^{-1}$ corresponding to the ring vibration band at 1597 cm.$^{-1}$ in pyridine itself. In the oxazolopyridine (VII) this band occurs at 1620 cm.$^{-1}$. In the di- and trihydroxypyridines, the phenylazo-compounds of type (III), and the *N*-methylation products, however, this band is either weak, occurs as a side-band, or is absent, thus providing further evidence that these compounds exist mainly in pyridone forms. Additional support for this conclusion is that all these compounds possess strong bands at 1626—1669 and 1506—1558 cm.$^{-1}$, characteristic of amide groups (Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," Van Nostrand, 1949, p. 20).

All the di- and tri-hydroxypyridines described above have been tested against a range of Gram-positive and Gram-negative organisms by Dr. A. S. Schlingman (Parke, Davis & Co., Detroit). At a concentration of 0·1 mg./c.c. these compounds were inactive with the exception of (I; R = R′ = Me) which partially inhibited the growth of *Neisseria catarrhalis*, *Micrococcus pyogenes* var. *aureus*, *Brucella suis*, and *Salmonella typhosa*.

## Experimental

**2 : 6-*Dihydroxy*-4-*methylpyridine Hydrochloride*.**—Ethyl α-cyano-β-methylglutaconate (63 g.; Rogerson and Thorpe, *J.*, 1905, **87**, 1687) was refluxed with concentrated hydrochloric acid (250 c.c.) for 4 hr. The solution was concentrated and, on cooling, the product crystallised. Recrystallisation from hydrochloric acid (100 c.c.; 5N) furnished needles (27 g.) of **2 : 6-*dihydroxy*-4-*methylpyridine hydrochloride dihydrate***, m. p. 222—224° with dehydration (preheated bath) (Found: C, 38·8; H, 6·4; N, 7·4; Cl, 18·3. $C_6H_5O_2NCl,2H_2O$ requires C, 39·2; H, 6·5;

N, 7·6; Cl, 19·3%). Infra-red spectrum (Nujol mull): max. at 3413, 2688, 1634, 1524, 1344, 1263, 1236, 1171, 1003, 903, and 824 cm.$^{-1}$.

A solution of the hydrochloride (1·0 g.) in water (5 c.c.) was just basified with dilute aqueous ammonia, a deep blue colour rapidly developing. A slight excess of glacial acetic acid was added and the product slowly separated. After 1 hr., the pale blue solid (0·4 g.), m. p. 194—196°, was filtered off (cf. Rogerson and Thorpe, *loc. cit.*, who give m. p. 194°). Recrystallisation from absolute ethanol containing acetic acid gave the pyridine as plates, m. p. 194—196°. Infra-red spectrum (Nujol mull): max. at 1650, 1597, 1539, 1520, 1299, *ca.* 1205 (broad), 1160, and 997 cm.$^{-1}$. Alternatively, aniline (2·5 g.) was added to a solution of the hydrochloride (5·0 g.) in the minimum volume of hot ethanol. After acidification with glacial acetic acid, the solution was cooled and the free base crystallised, (m. p. 191—193°; 3·0 g.). This procedure proved the more convenient, especially for larger-scale experiments, and readily gave a colourless product.

2 : 6-*Diacetoxy*-4-*methylpyridine*.—The foregoing hydrated hydrochloride (20 g.) was refluxed with acetic anhydride (200 c.c.) for 1·5 hr. Distillation of the solution furnished the *diacetate* (18·8 g.), b. p. 120—122°/0·5 mm., $n_D^{20}$ 1·4971, m. p. 62—62·5°. It separated from ether–light petroleum (b. p. 40—60°) in cubes, m. p. 62—62·5° (Found: C, 58·4; H, 5·4; N, 6·7. $C_{10}H_{11}O_4N$ requires C, 57·9; H, 5·3; N, 6·7%). Infra-red spectrum (film of super-cooled liquid): max. at 1770, 1613, 1563, 1433, 1407, 1368, 1319, 1208, 1172, 1144, 1047, 1018, 999, 973, 890, 842, 751, and 730 cm.$^{-1}$.

2 : 6-*Dihydroxy*-4-*methyl*-3-*phenylazopyridine*.—A solution of the foregoing hydrated hydrochloride (15 g.) in water (70 c.c.) was mixed with sodium acetate (70 g.) in water (100 c.c.), then treated with benzenediazonium chloride solution (from aniline, 7 g.). The crude azo-compound was separated, washed with water and methanol, and dried *in vacuo* (yield 17 g., 90%; m. p. 242—246°). The pure *azo*-compound, m. p. 251—252°, was obtained as fine, red needles by recrystallisation from methanol (Found: C, 62·7; H, 5·0; N, 17·9. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). Ultra-violet absorption spectrum (in ethanol): max. at 2590, 4130, and 4150 Å (ε 13,700, 34,000, and 33,000 respectively) and inflections at 2550 and 4110 Å (ε 13,200 and 33,700 respectively). Infra-red spectum (Nujol mull): max. at 3356, 1656, 1585, 1515, 1451, 1405, 1256, 1214, 895, 870, 809, and 757 cm.$^{-1}$.

2 : 6-*Diacetoxy*-3-*diacetylamino*-4-*methylpyridine*.—The foregoing azo-compound (13 g.) was added during 50 min. to a stirred mixture of zinc (24 g.), acetic acid (40 c.c.), and acetic anhydride (20 c.c.) at 10—15°; more zinc (6 g.), acetic acid (30 c.c.), and acetic anhydride (30 c.c.) were then added to accelerate the reduction. The mixture was shaken for 30 min. and filtered, the solids being washed with acetic acid (60 c.c.) followed by acetic anhydride (60 c.c.) to remove acetanilide. Extraction of the residue with boiling acetic anhydride (150 c.c.; 3 × 80 c.c.) and evaporation *in vacuo* furnished a gum which crystallised on trituration with ethyl methyl ketone. Repeated recrystallisation from the same solvent gave 2·0 g. of material, m. p. 145—155°.

The combined mother-liquors were evaporated and the residue refluxed for 3 hr. with acetic anhydride (150 c.c.). Evaporation and crystallisation of the residue from light petroleum (b. p. 60—80°)–ethyl methyl ketone (1 : 1) gave rectangular plates of 2 : 6-*diacetoxy*-3-*diacetylamino*-4-*methylpyridine* (6·6 g.; 42% allowing for the 2·0 g. of material removed), m. p. 142—143° (Found: C, 54·3, 54·6; H, 5·2, 5·2; N, 8·9, 8·9%; acetyl val., 52·2; *C*-Me, 22·0. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2; N, 9·1%; acetyl val. for 4 groups, 55·8; 5*C*-Me 24·4%). Infra-red spectrum (Nujol mull): max. at 1767, 1724, 1608, 1563, 1370, 1333, 1279, 1244, 1191, 1149, 1053, 1014, 986, 956, 908, 877, 862, 778, and 766 cm.$^{-1}$.

The material, m. p. 145—155°, was recrystallised repeatedly from ethyl methyl ketone, to give needles of 3-*acetamido*-2 : 6-*diacetoxy*-4-*methylpyridine*, m. p. 177—178° (Found: C, 53·6; H, 5·4; N, 10·1, 10·3. $C_{12}H_{14}O_5N_2$ requires C, 54·1; H, 5·3; N, 10·5%). The ultra-violet absorption spectrum of this compound in ethanol changed with time and, as preparation of the solution required a considerable time, owing to the slow dissolution in cold ethanol, extensive interaction may have occurred before the spectrum could be determined. The results on this solution were as follows: max. at 2675 and 3240 Å (ε 3100 and 6000); the values of ε after 6 hr. were 2900 and 6700, and after 24 hr. 2600 and 7100 respectively. Attempts to effect these changes on a preparative scale were unsuccessful as the substance could be recovered unchanged from cold ethanol and boiling with ethanol gave a purple gum. The infra-red spectrum of this compound (Nujol mull) had the following max.: 3268, 1773, 1656, 1608, 1518, 1370, 1284, 1192, 1149, 1057, 1018, 903, and 887 cm.$^{-1}$.

2 : 3 : 6 *Triacetoxy*-4-*methylpyridine*.—The diacetylamino-compound (15 g.) was refluxed for

1 hr. with concentrated hydrochloric acid (150 c.c.), and the solution evaporated to dryness *in vacuo*. The residue was warmed with acetic anhydride (150 c.c.) until the gum dissolved and the ammonium chloride was then removed by filtration. After refluxing for 1 hr., the filtrate was distilled to give the *triacetoxy*-compound (11·0 g., 85%) as a very viscous, almost colourless oil, b. p. 170—174°/0·9 mm., $n_D^{20}$ 1·4960 (Found: C, 53·7; H, 4·9; N, 4·7. $C_{13}H_{13}O_6N$ requires C, 53·9; H, 4·9; N, 5·2%). Infra-red spectrum (liquid film): max. at 1767, 1608, 1567, 1456, 1427, 1395, 1366, 1339, *ca.* 1220—1175, 1146, 1057, 1017, 988, 904, 877, 826, and 765 cm.$^{-1}$.

2 : 3 : 6-*Trihydroxy*-4-*methylpyridine Hydrochloride*.—The foregoing triacetate was hydrolysed for 1 hr. with boiling concentrated hydrochloric acid (100 c.c.). Evaporation under reduced pressure and recrystallisation from hydrochloric acid (8N) furnished colourless needles of 2 : 3 : 6-*trihydroxy*-4-*methylpyridine hydrochloride dihydrate*, m. p. 82—83° (Found: C, 34·2; H, 5·5; N, 6·6; Cl, 16·5. $C_6H_8O_3NCl,2H_2O$ requires C, 33·7; H, 5·7; N, 6·6; Cl, 16·6%). Infra-red spectrum (Nujol mull): max. at *ca.* 3200 (broad), 1645, 1553, 1435, 1377, 1302, 1241, 1009, 855, 807, and 741 cm.$^{-1}$.

Treatment of an aqueous solution with ferric chloride solution gave a deep purple colour which rapidly faded to yellow and then changed to dark red; excess of ferric chloride produced only a yellow colour. When an aqueous solution of the hydrochloride was shaken with sodium hydrogen carbonate solution a green colour developed on the surface, and when shaken in air the solution became dark blue. Ammoniacal silver nitrate solution gave an immediate black precipitate.

2 : 3 : 6-*Trihydroxy*-4-*methylpyridine*.—An ethereal diazomethane solution, prepared from methylnitrosourea (1·5 g.), potassium hydroxide solution (5 c.c., 50%), and ether (30 c.c.), was added to the hydrochloride (1·0 g.) dissolved in methanol (2 c.c.). The clear solution was immediately treated with acetic acid (1 c.c.) and, on cooling at 0°, the crude product slowly separated. Recrystallisation from ethanol furnished yellow prismatic needles of 2 : 3 : 6-*trihydroxy*-4-*methylpyridine* which sintered at 200—205° and decomposed without melting at higher temperatures (Found: C, 50·6; H, 4·8; N, 10·0. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). It became brown after a few hr. at room temperature.

2 : 6-*Diacetoxy*-3 : 4-*dimethylpyridine*.—Ethyl γ-cyano-αβ-dimethylglutaconate (Rogerson and Thorpe, *loc. cit.*; 125 g.) was refluxed with concentrated hydrochloric acid (450 c.c.) for 5 hr. and the solution evaporated almost to dryness. After addition of excess of aqueous ammonia, the mixture was distilled until the dihydroxypyridine began to sublime. The residue and sublimate were thoroughly washed with water containing a little acetic acid. Attempts to purify the resulting crude dihydroxypyridine by sublimation and recrystallisation failed. This material was therefore refluxed with acetic anhydride (300 c.c.) for 30 min. and then distilled, to give 2 : 6-*diacetoxy*-3 : 4-*dimethylpyridine* (82 g., 70%), oil, b. p. 136—140°/1 mm., $n_D^{20}$ 1·5033, m. p. 64—65°. Recrystallisation from water containing a little ethanol gave thin plates, m. p. 64—65° (Found: C, 58·8; H, 5·8; N, 6·8. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%). Infra-red spectrum (Nujol mull): max. at 1761, 1613, 1590, 1374, *ca.* 1200 (broad), 1147, 1083, 1027, and 885 cm.$^{-1}$.

On addition of ammonia to the original hydrolysis mixture and during the subsequent distillation a vivid blue colour developed, this effect being minimised by the use of acetic acid during the working up, as described. Similar blue or green colours have been observed during the preparation of di- and tri-hydroxypyridines by Rogerson and Thorpe and by Lapworth and Collie (*locc. cit.*). The hydrochlorides of compounds of type (II) are stable and can be kept for several months without change, but the corresponding free bases gradually become blue or brown, especially in soda-glass containers. These compounds give colourless solutions in aqueous sodium hydroxide, but ammoniacal solutions rapidly become blue.

2 : 6-*Dihydroxy*-3 : 4-*dimethylpyridine*.—The foregoing diacetate (82 g.) was refluxed for 1·5 hr. with concentrated hydrochloric acid (300 c.c.). On cooling, 2 : 6-*dihydroxy*-3 : 4-*dimethylpyridine hydrochloride hydrate* crystallised in plates, m. p. 93—94°, unchanged by recrystallisation from hydrochloric acid (5N) (Found: C, 42·6; H, 6·6; N, 6·9. $C_7H_{10}O_2NCl,H_2O$ requires C, 43·4; H, 6·2; N, 7·2%). Infra-red spectrum (Nujol mull): max. at 3448, 1639 (inflection at 1610), 1534, 1344, 1323, 1316, 1229, 1188, 1116, and 1003 cm.$^{-1}$.

When this material was heated at 50°/0·5 mm. for several hours it furnished 2 : 6-dihydroxy-3 : 4-dimethylpyridine, m. p. 188—190° (Found: C, 60·7; H, 6·7; N, 9·7. Calc. for $C_7H_9O_2N$: C, 60·4; H, 6·5; N, 10·1%). Rogerson and Thorpe (*loc. cit.*) give m. p. 189°. Infra-red spectrum (Nujol mull): max. at 1626, 1600 (side-band), 1580, 1539, 1490, 1372, 1306, 1205, 1183, and 996 cm.$^{-1}$.

2 : 6-*Dihydroxy*-3 : 4-*dimethyl*-5-*phenylazopyridine*.—By the method used for the preparation

of the monomethyl analogue, this compound was obtained in 64% yield. Recrystallisation from a large volume of methanol furnished red needles of the *azo*-compound, m. p. 255—256° (Found: C, 63·8; H, 5·3; N, 16·8. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%). Infra-red spectrum (Nujol mull): max. at 1650, 1587, 1506, 1456, 1372, 1247, 1199, 1171, 1157, 904, and 756 cm.$^{-1}$. Ultra-violet absorption spectrum (in ethanol): max. at 2550, 2600, 4140, and 4170 Å (ε, 14,500, 14,800, 35,500, and 35,600 respectively).

2 : 6-*Diacetoxy*-5-*diacetylamino*-3 : 4-*dimethylpyridine*.—The foregoing azo-compound (12·2 g.) was reduced with zinc (20 g.), acetic acid (60 c.c.), and acetic anhydride (40 c.c.) as in the previous case. The mixture was filtered and the solid washed with acetic acid (3 × 100 c.c.); evaporation of the combined filtrates gave a solid residue (23 g.) which was washed with boiling ether (3 × 100 c.c.). Part of the remaining fine powder (14 g.; m. p. 170—174°) was recrystallised repeatedly from ethyl methyl ketone. 2 : 6-*Diacetoxy*-5-*acetamido*-3 : 4-*dimethylpyridine* separated in threads, m. p. 197—198° (Found: C, 55·8; H, 5·8; N, 10·2. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·8; N, 10·0%). Infra-red spectrum (Nujol mull): max. at 3268, 1758, 1650, 1603, 1527, 1372, 1272, 1218, 1202, 1119, 1092, 1047, 1015, 928, 854, 795, and 717 cm.$^{-1}$. Like the lower homologue this compound interacted with ethanol during the measurement of the ultra-violet spectrum. The values obtained were: max. at 2700 and 3350 Å (ε 3200 and 3800 respectively); after 6 hr. the maximum at the lower wave-length had disappeared and a single maximum 3340 Å (ε 10,100) was found.

The remaining material (12 g.) was refluxed for 7 hr. with acetic anhydride (120 c.c.), and the excess of anhydride then removed *in vacuo*. Crystallisation of the residue from ether (50 c.c.) gave the product, m. p. 92—94° (8·8 g., 63% allowing for the portion removed). 2 : 6-*Diacetoxy*-5-*diacetylamino*-3 : 4-*dimethylpyridine* separated from ether in rectangular plates, m. p. 96—97° (Found: C, 55·6; H, 5·8; N, 8·8. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%). Infra-red spectrum (Nujol mull): max. at 1767, 1718, 1600, 1433, 1416, 1333, 1282, 1247, *ca.* 1190 (broad), 1131, 1091, 1055, 1037, 1016, 954, 922, and 877 cm.$^{-1}$.

The triacetyl compound, m. p. 197—198°, (0·5 g.), was refluxed with acetic anhydride (10 c.c.) for 7 hr. Isolated as before and crystallised from ether, the tetra-acetyl compound (0·5 g.) melted at 94—95°.

2 : 5 : 6-*Trihydroxy*-3 : 4-*dimethylpyridine Hydrochloride*.—Hydrolysis of the foregoing tetra-acetyl derivative (8·8 g.) and acetylation of the resulting triol, as in the case of the lower homologue, furnished 2 : 5 : 6-*triacetoxy*-3 : 4-*dimethylpyridine* (6·8 g., 88%) which distilled as a pale yellow, extremely viscous syrup, b. p. 175—177°/0·9 mm., $n_D^{20}$ 1·4988 (Found: C, 55·9; H, 5·5; N, 4·5. $C_{13}H_{15}O_6N$ requires C, 55·5; H, 5·4; N, 5·0%). Infra-red spectrum (liquid film): max. at 1770, 1605, 1435, 1410, 1370, *ca.* 1190 (broad), 1088, 1042, 1013, 952, 925, 876, 756, and 713 cm.$^{-1}$.

The triacetate (6·6 g.) was hydrolysed as in the previous case and the product crystallised from aqueous "AnalaR" hydrochloric acid (1 : 1). The *hydrochloride hydrate* separated as needles, m. p. 98—100° (with dehydration; preheated bath) (Found: C, 40·5; H, 5·9; N, 7·3; Cl, 15·4. $C_7H_{12}O_4NCl$ requires C, 40·1; H, 5·8; N, 6·7; Cl, 16·9%). Infra-red spectrum (Nujol mull): max. at 3356, 3205, 1736, 1669, 1623, 1543, 1381, 1289, 1259, 1174, 1095, 1046, and 894 cm.$^{-1}$. The acid solution gave an intense red colour with a trace of ferric chloride.

6-*Acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine*.—The azo-compound (III; R = R′ = Me) (20 g.) was reduced with zinc (40 g.), acetic acid (150 c.c.) and acetic anhydride (25 c.c.), the almost colourless solution being filtered after 1 hr. The residue obtained by evaporation of the filtrate *in vacuo* was refluxed with acetic anhydride (150 c.c.) for 30 min. Removal of the excess of anhydride furnished a gum which partly crystallised, trituration with ether giving small amounts of the crude tri- and tetra-acetyl compounds. The viscous residual gum was then distilled to give an oil, b. p. 160—180°/2 mm., which solidified on trituration with ether. After several recrystallisations from ether and ethyl methyl ketone–light petroleum (b. p. 60—80°), 6-*acetoxy*-4 : 5 : 2′-*trimethyloxazolo*(5′ : 4′-2 : 3)*pyridine* was obtained as prismatic needles, m. p. 119—120° [Found: C, 59·9; H, 5·6; N, 13·0%; acetyl val., 36·6. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%; acetyl val. (2 groups), 39·1]. Infra-red spectrum (Nujol mull): max. at 1748, 1621, 1567, 1362, 1258, 1208, 1110, 1087, 1063, 1012, 924, 912, and 868 cm.$^{-1}$. Ultra-violet absorption spectrum (in EtOH): max. at 2320 and 2790 Å (ε 8600 and 9700 respectively).

*Pyrolytic Distillation of* 5-*Acetamido*-2 : 6-*diacetoxy*-3 : 4-*dimethylpyridine*.—When the triacetyl compound was heated at 200—220°/*ca.* 5 mm. the oxazolopyridine sublimed in needles, m. p. 115—117° undepressed by admixture with the sample already described.

*Reaction of* 2 : 6-*Dihydroxy*-4-*methylpyridine with Diazomethane*.—Ethereal diazomethane,

prepared from methylnitrosourea (90 g.) by the method of Arndt (*Org. Synth.*, Coll. Vol. II, p. 166), was added gradually to an ice-cold suspension of the dihydroxypyridine (22·5 g.) in methanol (150 c.c.). After 21 hr. at room temperature, the dark green solution was evaporated and volatile product distilled under reduced pressure. Redistillation furnished **2 : 6-*dimethoxy*-4-*methylpyridine*** (9·9 g., 36%), b. p. 57°/2 mm., $n_D^{20}$ 1·5007, needles, m. p. 33—33·5° (Found : C, 62·9; H, 7·5; N, 9·3, $OCH_3$, 40·4. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1; $OCH_3$, 40·5%). Infra-red spectrum (liquid film) : max. at 2959, 1608, 1563, 1447, 1383, 1346, 1284, 1217, 1198, 1142, 1104, 1057, 991, 957, 925, and 821 cm.$^{-1}$.

Fractional crystallisation of the distillation residue furnished **6-*methoxy*-1 : 4-*dimethylpyrid*-2-*one*** (IX) as prismatic needles [from ethyl methyl ketone–light petroleum (b. p. 60—80°)], m. p. 92° (Found : C, 62·5; H, 7·4; N, 9·4; $OCH_3$, 18·8. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1; $OCH_3$, 20·3%) [infra-red spectrum (Nujol mull) : max. at 1656, 1580, 1531, 1401, 1263, 1242, 1189, 1171, 1131, 1037, 1027, 988, 923, 836, and 769 cm.$^{-1}$], and (?) **6-*methoxy*-4-*methylpyrid*-2-*one*** (X), plates (from ethyl methyl ketone), m. p. 170—171° (Found : C, 59·9; H, 6·2; N, 10·3; $OCH_3$, 20·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1; $OCH_3$, 22·1%) [infra-red spectrum (Nujol mull) : max. at 2688, 1650, 1605, 1558, 1427, 1357, 1248, 1155, 1094, 1034, 994, 966, 936, 839, and 775 cm.$^{-1}$].

*Demethylation of* **2 : 6-*Dimethoxy*-4-*methylpyridine***.—The dimethoxy-compound (0·7 g.) was refluxed for 5 hr. with concentrated hydrochloric acid (10 c.c.). On cooling, **2 : 6-dihydroxy-4-methylpyridine hydrochloride hydrate** crystallised, m. p. 217—219° (with dehydration; preheated bath), undepressed by admixture with authentic material.

*Methylation of* **2 : 6-*Dihydroxy*-3 : 4-*dimethylpyridine***.—(a) *With diazomethane*. The amine hydrochloride hydrate (12 g.) in methanol (40 c.c.) was left with ethereal diazomethane (from 60 g. of methylnitrosourea) at room temperature for 21 hr. After removal of the solvent, the volatile product was distilled, giving **2 : 6-*dimethoxy*-3 : 4-*dimethylpyridine*** (2·5 g.; 24%), b. p. 61—62°/0·9 mm., $n_D^{20}$ 1·5080, plates, m. p. 26—27° (Found : C, 64·7; H, 8·0; N, 8·4; $OCH_3$, 35·0. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8; N, 8·4; $OCH_3$, 37·2%). Infra-red spectrum (liquid film) : max. at 2967, 1608, 1575, *ca.* 1450 (broad), 1370, 1341, 1282, 1193, 1160, 1111, 1062, 1017, 963, 905, 829, 781, and 754 cm.$^{-1}$.

Repeated recrystallisation of the distillation residue from carbon tetrachloride and ethyl methyl ketone furnished (?) **6-*methoxy*-1 : 3 : 4-*trimethylpyrid*-2-*one*** (XII), rectangular plates (1·0 g.), m. p. 119—120° (Found : C, 64·3; H, 7·8; N, 8·3). $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8; N, 8·4%). Infra-red spectrum (Nujol mull) : max. at 1647, 1582, 1550, 1217, 1205, 1103, 1049, 1004, 938, 808, and 766 cm.$^{-1}$.

In one experiment a very small amount of (?) **6-*methoxy*-1 : 4 : 5-*trimethylpyrid*-2-*one*** (XIII), m. p. 85—87°, was also obtained by fractional crystallisation of the distillation residue (Found : C, 64·3; H, 7·4; N, 8·7%). Infra-red spectrum (Nujol mull): max. at 3125, 1639, 1603, 1585, 1546, 1266, 1208, 1183, 1168, 1104, 1004, 838, 774, and 765 cm.$^{-1}$.

(b) *With methyl sulphate*. To a boiling solution of the hydrochloride hydrate (20 g.) and sodium hydroxide (46 g.) in water (200 c.c.), methyl sulphate (140 g.) was added during 3 hr. with occasional additions of sodium hydroxide solution (10N) to keep the mixture alkaline. The solution was then refluxed for a further 30 min., cooled, and poured into ice-water (1 l.), the mixture being extracted four times with ether. After being washed with very dilute aqueous ammonia and water, the combined extracts were dried ($Na_2SO_4$) and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) yielded the methoxypyridone (0·9 g.), m. p. 118—120°, undepressed by admixture with the sample obtained in (*a*). The mother-liquors were distilled, to give the dimethoxy-compound (1·4 g.), b. p. 68°/1·5 mm., $n_D^{20}$ 1·5094.

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## 598. *The Preparation and Properties of Tellurium Dichloride.*

By E. E. Aynsley.

A convenient method of preparing tellurium dichloride by the reaction between Arcton 6 ($CF_2Cl_2$) and molten tellurium is given. Some of its properties are described. It has been used to prepare tellurium(IV) dichloride dibromide and some pyridine complexes, but attempts to prepare tellurium(IV) dichloride di-iodide were unsuccessful. The Arcton 6 is partly converted into $C_2F_4Cl_2$, presumably through the free radical $CF_2Cl$.

Previous evidence for tellurium dichloride is a little confused. From chlorine and hot tellurium, Rose (*Pogg. Ann.*, 1831, **21**, 443) obtained a mixture of the dichloride and tetrachloride from which he believed he separated the former by fractional distillation. The formation of the dichloride in other reactions has been noted by Lenher (*J. Amer. Chem. Soc.*, 1902, **24**, 188) and by Linder and Apolant (*Z. anorg. Chem.*, 1924, **136**, 381). But Damiens (*Ann. Chim.*, 1923, **19**, 44) found no evidence of tellurium dichloride from the freezing-point curve of mixtures of the constituent elements. He concluded that it exists only as a vapour, and that on solidification it dissociates into a mixture of the element with the tetrachloride. Later Grether (*Ann. Physik*, 1936, **26**, 1) measured atomic distances in tellurium dichloride by electron diffraction in the vapour and found them to be 2·55 Å, and Dharmatti (*Proc. Indian Acad. Sci.*, 1940, **12**, *A*, 212) made magnetic-susceptibility measurements on the compound; neither describes the preparation. As the latter author states that his material was very unstable and that some decomposition took place before he could make his measurements, it is difficult to know what he was actually handling.

Tellurium dichloride has been described as a black, amorphous solid which does not fume in air. When molten it is black and its vapour is purple. Michaelis (*Ber.*, 1887, **20**, 2488) gives m. p. 175° and b. p. 324°, but Carnelley and Williams (*J.*, 1879, 563; 1880, 125) found m. p. 209°±5°, b. p. 327°.

All the above methods of preparation produce mixtures from which the dichloride has to be separated by a tedious fractionation in which it is difficult to remove the last traces of tetrachloride.

Streaming Arcton 6 (dichlorodifluoromethane, $CF_2Cl_2$) over molten tellurium provides a new method of preparing tellurium dichloride, in a pure state and a good yield. This product melted sharply at 208° and boiled at 328° (corr.) in good agreement with Carnelley and Williams (*loc. cit.*). From the unpleasant-smelling gaseous by-products, small quantities of *s*-dichlorotetrafluoroethane were isolated, so, presumably the reaction involves:

$$\left.\begin{matrix}CF_2Cl_2\\CF_2Cl_2\end{matrix}\right\} + Te \longrightarrow \left.\begin{matrix}CF_2Cl\\CF_2Cl\end{matrix}\right\} + TeCl_2$$

and the radical $CF_2Cl$ at least in part.

The dichloride has been described as soluble in diethyl ether. But this is not true: tellurium dichloride disproportionates rapidly into tellurium and tellurium tetrachloride in diethyl ether, dioxan, or dibutyl ether. The solutions previously described were of the tetrachloride, not the dichloride. My attempt to form a complex between tellurium dichloride and pyridine failed because disproportionation takes place in this liquid also, giving tellurium and the yellow base, dipyridinetetrachlorotellurium(IV), $(C_5H_5N)_2TeCl_4$. Indeed I have not found a solvent in which tellurium dichloride does not disproportionate: in liquids like carbon tetrachloride it is insoluble.

When warmed in fluorine, very much diluted with nitrogen, tellurium dichloride is converted first into the tetrafluoride and then into the hexafluoride. No evidence has been obtained of the existence of a difluoride. When heated in chlorine, the dichloride is oxidised to the tetrachloride. Damiens (*loc. cit.*) found an ethereal solution of tellurium dichloride to absorb large amounts of bromine and iodine and took this as evidence for $TeCl_2Br_2$ and $TeCl_2I_2$ in solution, but he was unable to isolate either substance. Since tellurium dichloride disproportionates in diethyl ether, clearly Damiens must have started with a solution of the tetrachloride and not the dichloride, and the formation of either of these compounds

appears improbable. I have found that when excess of liquid bromine is added to tellurium dichloride, a strongly exothermic reaction occurs, and, on removal of the excess of bromine with carbon dioxide, the new compound tellurium(IV) dichloride dibromide, $TeCl_2Br_2$, is obtained as a yellow powder, m. p. 292°, b. p. 415° (corr.). The liquid is ruby-red and forms a dark-yellow crystalline mass on cooling; the vapour is orange. Like the tetrabromide, the compound is unaffected by dry air but slowly absorbs moisture from the atmosphere. Water decomposes it at once with the formation of a white precipitate of tellurous acid in hydrochloric and hydrobromic acids.

When ethereal solutions of tellurium(IV) dichloride dibromide and pyridine are mixed, a new complex, dipyridinedichlorodibromotellurium(IV), $(C_5H_5N)_2TeCl_2Br_2$, is precipitated as an amorphous cream-coloured powder. It is stable in dry air, but becomes yellow in moist air, and is at once hydrolysed by water to tellurous acid. It melts with decomposition, liberating pyridine and tellurium dichloride.

Dipyridinedichlorodibromotellurium(IV) readily dissolves in hot concentrated hydrochloric acid, from which, on cooling, separate pale-orange needles of a second new complex, dipyridinium tetrachlorodibromotellurite, $(C_5H_5NH)_2TeCl_4Br_2$. When this, or dipyridinedichlorodibromotellurium(IV), is dissolved in hot concentrated hydrobromic acid and the solution cooled, red needles of dipyridinium hexabromotellurite, $(C_5H_5NH)_2TeBr_6$, separate. This was first prepared by Lenher (*J. Amer. Chem. Soc.*, 1900, **22**, 136) from tellurium dioxide in hydrobromic acid and pyridine. When hydriodic is substituted for hydrobromic acid, a third new complex, dipyridinium hexaiodotellurite, $(C_5H_5NH)_2TeI_6$, is obtained as black needles.

In an attempt to prepare the salt, $(C_5H_5NH)_2TeF_2Cl_2Br_2$, dipyridinodichlorodibromotellurium(IV) was evaporated with a concentrated solution of hydrofluoric acid. The first crop of crystals was red needles of $(C_5H_5NH)TeBr_6$; the second, after further concentration, orange needle-shaped mixed crystals of $(C_5H_5NH)_2TeBr_6$ and $(C_5H_5NH)_2TeCl_6$; the third, after still further concentration, yellow needles of $(C_5H_5NH)_2TeCl_6$. From this last compound, dipyridinium hexachlorotellurite, all the chlorine is replaced by bromine under the action of hot concentrated hydrobromic acid, giving red crystals of dipyridinium hexabromotellurite. Similarly, solutions of dipyridinium hexachlorotellurite and hexabromotellurite, when treated with hot concentrated hydriodic acid, yield black needles of the hexaiodo-compound. Clearly the stabilities of these complexes increase in the order chloro-, bromo-, iodo-tellurite. Attempts to prepare tellurium(IV) dichloride di-iodide were unsuccessful.

Neither gaseous nor liquid sulphur dioxide reacts with tellurium dichloride. Gaseous dinitrogen tetroxide has no immediate action, but the liquid oxidises it to tellurium dioxide, nitrosyl chloride being also formed, thus: $TeCl_2 + N_2O_4 \longrightarrow TeO_2 + 2NOCl$.

Ammonia, at about its temperature of condensation, is rapidly absorbed by tellurium dichloride which increases greatly in bulk. The black powder remaining when the excess of ammonia is removed is unaffected by ordinary air and contains 15% of combined ammonia, at least partly as ammonium chloride. In liquid ammonia, however, the dichloride first swells to a bulky mass, but with further liquid collapses to a fine powder. This is tellurium; the liquid ammonia contains ammonium chloride, and nitrogen is liberated. Quantitative observations show that the reaction can be represented thus: $3TeCl_2 + 8NH_3 \longrightarrow 3Te + 6NH_4Cl + N_2$.

## Experimental

*Preparation of Tellurium Dichloride.*—Arcton 6 ($CF_2Cl_2$) (from Imperial Chemical Industries Limited), dried first with concentrated sulphuric acid and then with phosphoric oxide, was led over molten tellurium contained in the first section of a 2·5-cm. Pyrex tube, constricted at intervals of about 10 cm. to furnish six compartments. A receiver was attached to the far end and was protected by a drying tube. The tellurium dichloride was distilled forward in the gas stream from section to section and finally into the receiver. In this way material entirely free from unchanged tellurium and the tetrachloride could be collected at a rate of 2 g. per hr. (Found: Te, 64·5; Cl, 35·6. Calc. for $TeCl_2$: Te, 64·3; Cl, 35·7%).

When the gas issuing from the receiver was cooled to −20° (Arcton 6 has b. p. −29·8°),

about 1 ml. of a colourless liquid containing carbon, chlorine, fluorine, and traces of tellurium was collected. The nature and quantity of the liquid appeared to depend on the temperature of the tellurium. Fractionation gave a little liquid, b. p. 4°, which produced tetrafluoroethylene with zinc and alcohol and so was *s*-dichlorotetrafluoroethane. A higher-boiling, foul-smelling fraction containing traces of tellurium was always obtained and sometimes a fraction boiling between $-6°$ and $+6°$ : these are under examination.

*Disproportionation of Tellurium Dichloride.*—Tellurium dichloride was distilled into a tube fitted with a fritted-glass filter, and its weight was obtained. Dry diethyl ether was continuously drawn through the dichloride for ½ hr., followed by warm, dry nitrogen. The weight of the residue of tellurium and that of the tellurium tetrachloride in the ether corresponded to the disproportionation $2TeCl_2 \longrightarrow Te + TeCl_4$. When ether was added to hard lumps of tellurium dichloride they rapidly crumbled to finely divided tellurium and left tetrachloride in the ethereal layer. Behaviour was similar with dioxan and dibutyl ether.

Disproportionation occurred in dry pyridine, the products being tellurium and yellow dipyridinetetrachlorotellurium(IV). A little of this was separated from the tellurium by extraction with hot pyridine, and, although the complex was not obtained pure, it was readily identified by dissolving it in hot concentrated hydrochloric acid and crystallising out yellow needles of dipyridinium hexachlorotellurite [Found : C, 23·8; N, 5·7; H, 2·6; Te, 25·8; Cl, 42·3. Calc. for $(C_5H_5NH)_2TeCl_6$ : C, 24·0; N, 5·6; H, 2·4; Te, 25·5; Cl, 42·6%].

*Reactions with Halogens.*—Gently warmed tellurium dichloride in fluorine diluted with nitrogen (1 : 9, by vol.) reacted quietly without further heating. The surface of the solid was soon coated with the tetrafluoride. When the temperature was raised or the proportion of fluorine in the gas mixture increased, the tetrafluoride was immediately oxidised to gaseous tellurium hexafluoride.

Chlorine rapidly converted molten tellurium dichloride into the tetrachloride which was collected as a snow-white crystalline mass.

Excess of liquid bromine was added to a few g. of tellurium dichloride. A strongly exothermic reaction took place. On removal of the excess of bromine with a stream of carbon dioxide, the yellow powder *tellurium*(IV) *dichloride dibromide* (Found : Te, 35·9; Cl, 19·5; Br, 44·9. $TeCl_2Br_2$ requires Te, 35·6; Cl, 19·8; Br, 44·6%), m. p. 292°, b. p. 415° (corr.), remained. Slight decomposition takes place on boiling.

The following attempts failed to produce tellurium(IV) dichloride di-iodide : (*a*) passing iodine vapour over molten tellurium dichloride, (*b*) keeping tellurium dichloride in a saturated solution of iodine in carbon tetrachloride, (*c*) sealing tellurium dichloride and iodine in an evacuated tube, and (*d*) mixing ethereal solutions of tellurium dichloride dibromide and iodine.

*Pyridine Complexes of* $TeCl_2Br_2$.—This compound (1 mol.) and pyridine (2 mols.) were mixed in ether. The compound *dipyridinedichlorodibromotellurium*(IV) was precipitated as a cream-coloured amorphous solid in almost quantitative yield [Found : C, 23·0; N, 5·6; H, 2·2; Te, 24·5; Cl, 13·6; Br, 31·2. $(C_5H_5N)_2TeCl_2Br_2$ requires C, 23·2; N, 5·4; H, 1·9; Te, 24·7; Cl, 13·8; Br, 31·0%]. This compound is at once hydrolysed by water to tellurous acid. It melts with decomposition and, on boiling, pyridine and tellurium dichloride are evolved.

Dipyridinedichlorodibromotellurium(IV) was dissolved in hot concentrated hydrochloric acid and, on cooling, pale orange needles of *dipyridinium tetrachlorodibromotellurite* crystallised [Found : C, 20·1; N, 4·9; H, 2·3; Te, 21·5; Cl, 24·4; Br, 26·9. $(C_5H_5NH)_2TeCl_4Br_2$ requires C, 20·4; N, 4·8; H, 2·0; Te, 21·7; Cl, 24·1; Br, 27·1%].

Both the dipyridine compound and the salt dissolve in hot concentrated hydrobromic acid and in hot concentrated hydriodic acid, giving red needles of dipyridinium hexabromo- and black needles of *hexaiodo-tellurite* respectively [Found : C, 11·5; N, 2·4; H, 1·2; Te, 12·7; I, 72·0. $(C_5H_5NH)_2TeI_6$ requires C, 11·4; N, 2·7; H, 1·1; Te, 12·1; I, 72·6%].

An attempt to prepare $(C_5H_5NH)_2TeF_2Cl_2Br_2$ failed. When a solution of dipyridinedichlorodibromotellurium(IV) in concentrated hydrofluoric acid was concentrated on the water-bath, red crystals of the hexabromotellurite first crystallised on cooling. These were removed and the evaporation was continued, whereupon orange crystals were obtained which appeared to be mixed crystals of the hexabromo- and hexachloro-tellurite, since the crystals were homogeneous and contained bromine and chlorine but not in the proportion required for $(C_5H_5NH)_2TeCl_4Br_2$. The remaining solution on further concentration and cooling left yellow crystals of the hexachlorotellurite almost entirely free from bromine. Further, the hexachlorotellurite in hot concentrated hydrobromic acid deposited the hexabromotellurite on cooling, and both the chloro- and the bromo-compound when dissolved in hot concentrated hydriodic acid gave black needles of the hexaiodotellurite on cooling.

*Reaction with Dinitrogen Tetroxide.*—Dinitrogen tetroxide, redistilled from phosphoric oxide, was condensed on a known weight of tellurium dichloride and left for some hr. Removing the excess of tetroxide left a white residue of tellurium oxide which was weighed. All the chlorine was found in the distillate as nitrosyl chloride. The quantity of tellurium dioxide formed was in accordance with the equation, $TeCl_2 + N_2O_4 \longrightarrow TeO_2 + 2NOCl$.

*Reaction with Ammonia.*—(*a*) A stream of gaseous ammonia was passed for about 1 hr. over tellurium dichloride at −20°. The chloride rapidly swelled to many times its original volume. On removal of the excess of ammonia with dry nitrogen followed by exposure to phosphoric oxide in a desiccator, a black powder, unchanged when exposed to air and containing 15% of combined ammonia, was left. This substance was not, however, a pure material, and *X*-ray examination showed it to contain, among other things, ammonium chloride. (*b*) A weighed quantity of tellurium dichloride was placed on a fritted-glass filter in a Pyrex vessel, which was evacuated and cooled to −50° (b. p. $NH_3$, −33·5°), and then ammonia was led in. At first the ammonia was rapidly absorbed by the dichloride which swelled greatly, but when liquid ammonia began to appear in the vessel the bulky solid collapsed to a fine black solid on the filter. The ammonia filtrate passing through the filter was collected in a weighed vessel and, when the excess of ammonia had been removed from the apparatus, the black residue on the filter and the white residue from the filtrate were weighed. Elementary nitrogen was present in the ammonia leaving the reaction vessel; the black substance proved to be tellurium and the white one ammonium chloride, weights being in accordance with the equation $3TeCl_2 + 8NH_3 \longrightarrow 3Te + 6NH_4Cl + N_2$.

The author thanks Mr. G. N. Cutter for assistance with some of the practical work.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, May 14th,* 1953.]

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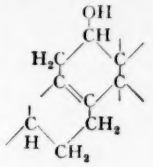
## 599. *The Chemistry of the Triterpenes and Related Compounds. Part XIX.* Further Evidence concerning the Structure of Polyporenic Acid A.*

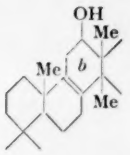
By T. G. HALSALL, R. HODGES, and E. R. H. JONES.

The nature of the side-chain of polyporenic acid A has been investigated by oxidative degradation, and the environment of the hydroxyl group in ring A has been elucidated. The results obtained, taken in conjunction with earlier work, suggest that the acid has the structure (XXII), *i.e.*, 3α : 12α-dihydroxyeburico-8 : 24(28)-dien-26-oic acid.

POLYPORENIC ACID A has been shown to be a tetracyclic diethenoid dihydroxy-carboxylic acid and to possess partial structure (I) (Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457; Jones and Woods, *J.*, 1953, 464; Halsall, Jones, and Lemin, *J.*, 1953, 468) which, it was suggested, might be expanded to (II).

(I)



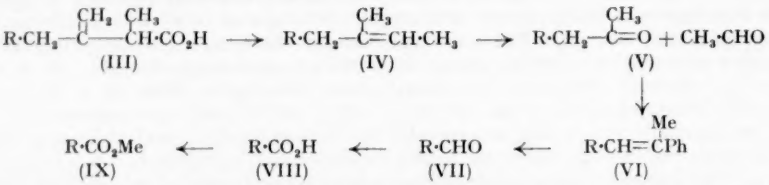




(II)

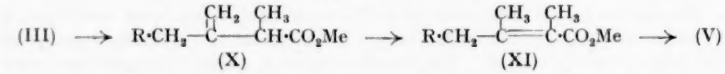
Polyporenic acid A is readily decarboxylated on melting, in a manner typical of αβ-unsaturated acids, giving a decarboxy-compound. By a series of degradations starting from the diacetate of the decarboxy-compound it has now been shown that the grouping (III) is present in polyporenic acid A. The *ab*-diacetate of the decarboxy-compound (IV) gave acetaldehyde and the methyl ketone (V) on ozonolysis. The latter product was treated with phenylmagnesium bromide, followed by acetic anhydride and sodium acetate, and so yielded the styryl derivative (VI). This had an ultra-violet absorption

* Part XVIII, *J.*, 1953, 2548.

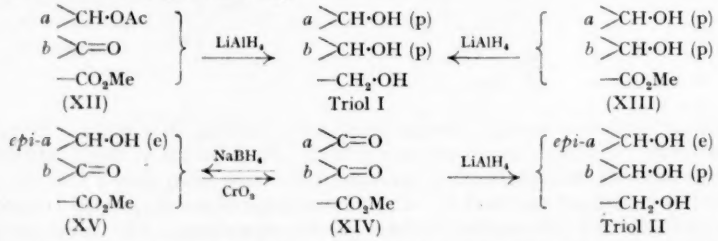
maximum at 2460 Å ($\varepsilon = 15{,}500$) (bands at higher wave-lengths being absent), typical of an α-substituted styrene (Hirschberg, *J. Amer. Chem. Soc.*, **1949**, **71**, 3241). On ozonolysis it gave acetophenone and a product which was oxidised directly with chromic acid under mild conditions to an acid (VIII), characterised as its methyl ester (IX). Analysis of the ester indicated that five carbon atoms had been removed during the degradation of polyporenic acid A to (VIII). The initial product of the ozonolysis of the styryl derivative must therefore be the aldehyde (VII).



When methyl polyporenate A (partial formula X) was heated with 5% methanolic potassium hydroxide, part of it was hydrolysed to polyporenic acid A. In the unhydrolysed ester the double bond situated βγ- to the methoxycarbonyl group moved into conjugation, and an αβ-unsaturated ester, methyl *iso*polyporenate A (partial formula XI), resulted. This formulation of the *iso*-ester was supported by light-absorption data and confirmed by ozonolysis of its diacetate, the methyl ketone (V) described above being obtained. A similar partial conversion into the corresponding *iso*-compound was obtained with methyl *b*-oxopolyporenate A *a*-acetate. The simultaneous formation of polyporenic acid A and methyl *iso*polyporenate is explained by assuming that methyl polyporenate A can either undergo hydrolysis to the carboxylate ion of acid A which does not rearrange, or be converted into the *iso*-ester which is much more difficult to hydrolyse than its precursor. With the isolation of methyl *iso*polyporenate A many puzzling features of the effect of hot alkali on derivatives of methyl polyporenate A, which had hitherto been encountered, were explained. Methyl polyporenate A can be satisfactorily hydrolysed to acid A by cold methanolic potassium hydroxide (cf. Curtis, Heilbron, Jones, and Woods, *loc. cit.*).

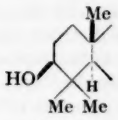


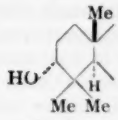
The reduction of methyl *b*-oxopolyporenate A *a*-acetate (XII) was attempted with both lithium aluminium hydride and sodium borohydride. The former gave a triol (triol I), identical with that already obtained by similar reduction of methyl polyporenate A (XIII) (Curtis, Heilbron, Jones, and Woods, *loc. cit.*). Hence reduction of the *b*-keto-group gives a hydroxyl group with the same configuration as the *b*-hydroxyl group originally present in polyporenic acid A. No reduction occurred with sodium borohydride. This confirms the hindered nature of the *b*-keto-group already indicated by earlier evidence, and suggests that the *b*-hydroxy-group arising from the lithium aluminium hydride reduction is polar (cf. Barton and Holness, *J.*, 1952, 83).



When methyl *a* : *b*-dioxopolyporenate A (XIV) was reduced with lithium aluminium hydride a different triol (triol II) was obtained. Therefore reduction of the *a*-keto-group leads to a hydroxyl group with a configuration *different* from that of the original *a*-hydroxyl

group of polyporenic acid A. Since the *a*-keto-group is not hindered (cf. oxime formation), the *a*-hydroxyl group in triol II is probably equatorial, and hence the parent *a*-hydroxyl group in polyporenic acid A is probably polar. Reduction of the *ab*-diketo-ester with sodium borohydride gave a *new* hydroxyketo-ester (XV), not identical with methyl *a*-hydroxy-*b*-oxopolyporenate A, which also must have an epimeric *a*-hydroxyl group, *i.e.*, it is methyl *epi-a*-hydroxy-*b*-oxopolyporenate A. Treatment of this compound with phosphorus pentachloride resulted in the retropinacolinic dehydration characteristic of

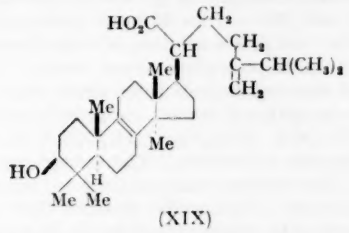

(XVI)

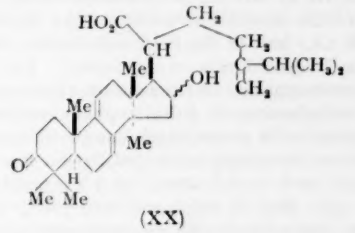

(XVII)

(XVIII)

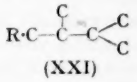
normal triterpenes with partial structure (XVI), since the product gave acetone on ozonolysis. The grouping (XVI) is therefore likely in the *epi-a*-acid, and the abnormal arrangement (XVII) in polyporenic acid A itself. The fact that dehydration of methyl *b*-oxopolyporenate A with phosphorus oxychloride yielded a product (XVIII), which gave only formaldehyde (from the unsaturated side-chain) on ozonolysis, supports this conclusion.

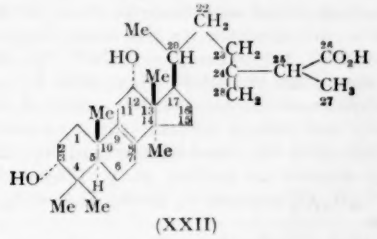
In the previous publications on polyporenic acid A, $C_{30}H_{48}O_4$ has been used as the provisional working formula although, as explained by Curtis, Heilbron, Jones, and Woods (*loc. cit.*), this did not imply our acceptance of it over the formula $C_{31}H_{50}O_4$, for which substantial evidence existed. The structures of two obviously related fungal acids, eburicoic acid and polyporenic acid C have now been elucidated. Both have been shown to be $C_{31}$ acids, eburicoic acid having structure (XIX) (Holker, Powell, Robertson, Simes, Wright, and Gascoigne, *J.*, 1953, 2422) and polyporenic acid C structure (XX) (Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548). The identical side-chains of these acids


(XIX)


(XX)

contain the six-carbon grouping (XXI) known to be present in polyporenic acid A. On the assumption that polyporenic acid A is synthesised by the same general biogenetic route as eburicoic acid and polyporenic acid C, combination of the partial structures (II), (III), and (XVII) leads to structure (XXII) [3α : 12α-dihydroxyeburico-8 : 24(28)-dien-26-oic acid] which is provisionally suggested for polyporenic acid A.


(XXI)


(XXII)

Experiments designed to convert polyporenic acid A into a derivative of lanosterol are in progress.

## Experimental

Rotations were determined in chloroform. M. p.s were determined on a Kofler block and are corrected. Alumina of activity I—II was employed for all chromatograms, and the light petroleum used for elution was the fraction of b. p. 60—80°. The derivatives of polyporenic acid A used as starting materials were prepared according to the methods described by Curtis, Heilbron, Jones, and Woods (*loc. cit.*).

*Ozonolysis of the* ab-*Diacetate of Decarboxylated Polyporenic Acid A.*—Ozonised oxygen (6%) was passed through a solution of the diacetate (1·9 g.) in acetic acid (15 c.c.) for 75 min. After addition of water (30 c.c.) half of the reaction mixture was distilled into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride in methanol. The 2 : 4-dinitrophenylhydrazone formed (420 mg.) was isolated, dissolved in benzene, and chromatographed on alumina. It was then repeatedly crystallised from methanol, to give orange-yellow needles of acetaldehyde 2 : 4-dinitrophenylhydrazone (mixed dimorphic forms), m. p. 146—160°. On admixture with the higher-melting dimorphic form it began to melt at 146°, partly resolidified, and finally melted at 168° (Found : N, 24·75. Calc. for $C_8H_8O_4N_4$ : N, 25·0%). Ether-extraction of the solution remaining after distillation yielded a product which was washed with alkali, and then adsorbed from light petroleum on alumina (150 g.). The fraction eluted with benzene–ether (1 : 1) crystallised from methanol, giving needles of the *methyl ketone* (V) (1·26 g.), m. p. 196—198°, raised by further crystallisation from methanol to 201—202°, $[\alpha]_D^{18}$ +85° (*c*, 0·7) (Found : C, 74·85; H, 9·85. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%).

*Preparation of the Styryl Derivative* (VI).—The methyl ketone (V) (3·0 g.) in ether (100 c.c.) was slowly added to phenylmagnesium bromide (6 g.) in ether (150 c.c.), and then the mixture was heated under reflux for 30 min. The product was worked up in the usual way, chromatographed on alumina in benzene, and then heated under reflux with acetic anhydride (15 c.c.) and sodium acetate (0·5 g.) for 1 hr. After dilution with water, ether-extraction yielded a product which was adsorbed on alumina (200 g.) from light petroleum. Elution with light petroleum–benzene (3 : 7) gave the *styryl* derivative (VI) (1·1 g.) which crystallised from methanol as flat prisms, m. p. 173—174°, $[\alpha]_D^{19}$ +80° (*c*, 1·8) (Found : C, 79·5; H, 9·4. $C_{38}H_{54}O_4$ requires C, 79·4; H, 9·45%). Light absorption in EtOH : Max., 2460 Å; $\varepsilon$ = 15,500.

*Ozonolysis of the Styryl Derivative* (VI).—Ozonised oxygen (6%) was passed through a solution of the styryl derivative (1·0 g.) in acetic acid (30 c.c.) for 35 min. After addition of water (80 c.c.) half of the reaction mixture was distilled into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride in methanol. The 2 : 4-dinitrophenylhydrazone formed (310 mg.) was chromatographed in benzene on alumina, and then crystallised three times from benzene, to give acetophenone 2 : 4-dinitrophenylhydrazone as dark-red needles, m. p. 247°, undepressed on admixture with an authentic sample (Found : N, 18·3. Calc. for $C_{14}H_{12}O_4N_4$ : N, 18·65%). The solution remaining after distillation was extracted with ether. The extract was washed with alkali and water, dried, and evaporated. The residue was oxidised in acetone with chromic acid (8N) in sulphuric acid (25% v/v) at 30°. The acidic product (150 mg.) was separated, methylated with diazomethane, and purified by chromatography on alumina (15 g.). Elution with benzene–ether (1 : 1) followed by crystallisation from aqueous methanol gave flat needles of the *methyl* ester (IX), m. p. 197°, $[\alpha]_D^{17}$ +90° (*c*, 0·55) (Found : C, 70·9; H, 9·2. $C_{31}H_{48}O_6 \cdot \frac{1}{2}CH_3 \cdot OH$ requires C, 71·05; H, 9·45%).

*Methyl* iso*Polyporenate A.*—A solution of methyl polyporenate A (10 g.) in 5% methanolic potassium hydroxide (200 c.c.) was heated under reflux for 25 min. After dilution with water, ether-extraction yielded a product (4·4 g.) which was adsorbed from benzene on alumina (400 g.). The fraction eluted with benzene–ether (1 : 4) was crystallised from methanol and then repeatedly from nitromethane, to give *methyl* iso*polyporenate A* as needles (1·11 g.), m. p. 164—165°, $[\alpha]_D^{18}$ +52° (*c*, 0·98) (Found : C, 76·7; H, 10·45. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). Light absorption in EtOH : Max., 2260 Å; $\varepsilon$ = 8000.

*Methyl* iso*Polyporenate A* ab-*Diacetate.*—Methyl *iso*polyporenate A (800 mg.), acetic anhydride (10 c.c.), and sodium acetate (250 mg.) were heated under reflux for 1 hr. The product was worked up in the usual manner and crystallised from ethanol, to give *methyl* iso*polyporenate A* ab-*diacetate* as needles, m. p. 126·5—127·5°, $[\alpha]_D^{18}$ +64° (*c*, 1·9) (Found : C, 73·75; H, 9·7. $C_{36}H_{56}O_6$ requires C, 73·95; H, 9·65%). Light absorption in EtOH : Max., 2260 Å; $\varepsilon$ = 8900.

*Ozonolysis of Methyl* iso*Polyporenate A* ab-*Diacetate.*—Ozonised oxygen (6%) was passed through a solution of the diacetate (400 mg.) in acetic acid (10 c.c.) for 20 min. Water (20 c.c.) was then added and the solution heated on the steam-bath for 10 min. Ether-extraction

yielded a product which was adsorbed from benzene on alumina (40 g.) and eluted with benzene–ether (1 : 1), to give the methyl ketone (V) (210 mg.) which crystallised from methanol as needles, $[\alpha]_D^{19}$ +83° (*c*, 0·5), m. p. 198—199° undepressed on admixture with an authentic sample.

*Hydrolysis of Methyl* b-*Oxopolyporenate A* a-*Acetate*.—Methyl *b*-oxopolyporenate A *a*-acetate (230 mg.) was heated under reflux in 5% methanolic potassium hydroxide (10 c.c.) for 20 min. After dilution with water, ether-extraction yielded a product which was separated into neutral (93 mg.) and acidic (131 mg.) fractions. The acidic fraction on methylation with diazomethane gave methyl *b*-ketopolyporenate A, m. p. 160—161°, undepressed on admixture with an authentic sample. The neutral fraction after four recrystallisations from methanol yielded *methyl* b-*oxoisopolyporenate A* as needles, m. p. 171—171·5°, $[\alpha]_D^{19}$ +47° (*c*, 0·62) (Found: C, 76·7; H, 10·3. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). Light absorption in EtOH: Max. 2260 Å; $\varepsilon = 9200$.

*Methyl* ab-*Dioxoisopolyporenate A*.—Methyl *iso*polyporenate A in acetone (20 c.c.) was oxidised with chromic acid (8N) in sulphuric acid (25% v/v) at 30°. The product was adsorbed from benzene on alumina (15 g.) and eluted with benzene–ether (1 : 4), to give *methyl* ab-*dioxoisopolyporenate A*, which crystallised from methanol as plates, m. p. 144·5—145·5°, $[\alpha]_D^{18}$ +72° (*c*, 1·5) (Found: C, 77·3; H, 9·85. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·75%). Light absorption in EtOH: Max., 2260 Å; $\varepsilon = 9400$. Oxidation of methyl *b*-oxo*iso*polyporenate A (40 mg.) in acetone (10 c.c.) in the same manner also gave methyl *ab*-dioxo*iso*polyporenate A, m. p. 145°, undepressed on admixture with a sample prepared from methyl *iso*polyporenate A.

*Reduction of Methyl* b-*Oxopolyporenate A* a-*Acetate*.—A solution of methyl *b*-oxopolyporenate A *a*-acetate (525 mg.) in ether (20 c.c.) was slowly added to lithium aluminium hydride (250 mg.) in ether (20 c.c.). The mixture was heated under reflux for 15 min., poured into dilute sulphuric acid, and extracted with chloroform. The extracted product was adsorbed from chloroform–benzene (1 : 1) on alumina (50 g.), eluted with chloroform–benzene (4 : 1), and crystallised from methanol as short prisms (385 mg.), $[\alpha]_D^{20}$ +61° (*c*, 0·65), m. p. 172—173, undepressed on admixture with a sample of the triol (" triol I ") prepared by Curtis, Heilbron, Jones, and Woods (*loc. cit.*) from methyl polyporenate A.

*Reduction of Methyl* ab-*Dioxopolyporenate A*.—Methyl *ab*-dioxopolyporenate A (1 g.) was reduced by lithium aluminium hydride (650 mg.) in the manner described above. " Triol II " was recrystallised four times from methanol, forming fine needles (680 mg.), m. p. 216—216·5°, $[\alpha]_D^{19}$ +86° (*c*, 0·88 in pyridine) (Found: C, 78·6; H, 10·6. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%).

*Reduction of Methyl* ab-*Dioxopolyporenate A by Sodium Borohydride*.—A solution of methyl *ab*-dioxopolyporenate A (4 g.) and sodium borohydride (375 mg.) in 1% aqueous dioxan (100 c.c.) was kept at 20° for 1 hr. Dilution with water yielded a precipitate which was filtered off and then adsorbed from benzene on alumina (200 g.). Elution with benzene–ether (1·4) gave *methyl* epi-a-*hydroxy*-b-*oxopolyporenate A* (3·8 g.), m. p. 172—175°, raised by crystallisation from methanol and from nitromethane to 175·5—176·5°, $[\alpha]_D^{19}$ +93° (*c*, 1·05) (Found: C, 77·0; H, 9·95. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). Reduction of methyl *epi-a*-hydroxy-*b*-oxopolyporenate A with lithium aluminium hydride in the manner described above gave " triol-II," m. p. 216°.

*Oxidation of Methyl* epi-a-*Hydroxy*-b-*oxopolyporenate A*.—Methyl *epi-a*-hydroxy-*b*-oxopolyporenate A (200 mg.) in acetone (10 c.c.) was oxidised with chromic acid solution (8N) in the usual manner. The product was adsorbed from benzene on alumina (20 g.), eluted with benzene–ether (1 : 1), and crystallised from methanol, to give needles of methyl *ab*-dioxopolyporenate A (150 mg.), $[\alpha]_D^{19}$ +103° (*c*, 0·78), m. p. 128—130°, undepressed on admixture with an authentic specimen.

*Dehydration of Methyl* b-*Oxopolyporenate A*.—Phosphorus oxychloride (0·5 c.c.) was added to a solution of methyl *b*-oxopolyporenate A (142 mg.) in pyridine at 0°. After being kept at 20° for 7 days the mixture was poured on ice. Ether-extraction yielded a *product* which crystallised from methanol as plates (78 mg.), m. p. 109—111°, raised by further crystallisation from ethanol to 117—117·5°, $[\alpha]_D^{18}$ +152° (*c*, 0·73) (Found: C, 79·9; H, 9·95. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·05%).

*Ozonolysis of the Phosphorus Oxychloride Dehydration Product of Methyl* b-*Oxopolyporenate A*.—Ozonised oxygen (6%) was passed through a solution of the dehydration product (400 mg.) in acetic acid (25 c.c.) for 30 min. After addition of water the volatile fragments were steam-distilled, first into a solution of dimedone in aqueous methanol, and then into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride in methanol. Formaldehyde dimethone (55 mg.)

m. p. 189°, undepressed on admixture with an authentic specimen, separated from the dimedone solution. No 2 : 4-dinitrophenylhydrazone was formed.

*Dehydration of Methyl* epi-a-*Hydroxy*-b-*oxopolyporenate A*.—Phosphorus pentachloride (150 mg.) was shaken with a suspension of methyl *epi-a*-hydroxy-*b*-oxopolyporenate A (250 mg.) in dry light petroleum (25 c.c.) for 15 min., by which time only the excess of phosphorus pentachloride remained undissolved. The solution was washed with water and alkali, dried, and evaporated to dryness. The product was adsorbed from benzene–light petroleum (1 : 1) on alumina (25 g.). Elution with benzene–ether (9 : 1) gave an oil which crystallised from methanol. The crystals (180 mg.) were crystallised four times from methanol, to give the dehydration *product* as needles, m. p. 102·5—103·5°, $[\alpha]_D^{18}$ +110° (*c*, 2·6) (Found: C, 79·75; H, 10·2. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·05%).

*Ozonolysis of the Phosphorus Pentachloride Dehydration Product of Methyl* epi-a-*Hydroxy*-b-*oxopolyporenate A*.—Ozonised oxygen (6%) was passed through a solution of the dehydration product (750 mg.) in acetic acid (20 c.c.) for 1 hr. After addition of water the volatile products were steam-distilled into a solution of dimedone in aqueous methanol. No derivative separated. The dimedone solution was then steam-distilled and the distillate passed into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride in methanol. After dilution with water, the 2 : 4-dinitrophenylhydrazone formed was extracted with benzene and then chromatographed on alumina with benzene. Acetone 2 : 4-dinitrophenylhydrazone was eluted and crystallised from ethanol as flat needles (264 mg., 72% yield), m. p. and mixed m. p. 126° (Found: N, 23·3. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%).

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THE UNIVERSITY, MANCHESTER, 13. [*Received, May 15th*, 1953.]

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## 600. *The Chemistry of the Triterpenes and Related Compounds. Part XX.* The Stereochemistry of Ring* E *of Betulin and Related Compounds.*

By (MISS) JOYCE M. GUIDER, T. G. HALSALL, and E. R. H. JONES.

The stereochemical course of the conversion of betulin into the anhydride (VI) has been investigated and clarified.

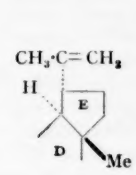
THE stereochemistry of ring E of lupeol has recently been shown to be represented by the partial formula (I) (Halsall, Jones, and Meakins, *J.*, 1952, 2862) with the *iso*propenyl group at $C_{(19)}$ and the hydrogen atom at $C_{(18)}$ both *trans* to the $C_{(17)}$ methyl group. β-Amyrin has now been shown to be (II) (olean-12-en-3β-ol) † (Barton and Holness, *J.*, 1952, 78; Klyne, *J.*, 1952, 2916; Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325). Structure (III) follows for germanicol (olean-18-en-3β-ol) (Barton and Brooks, *J.*, 1951, 257) and hence (IV; R = H, R′ = Me) for lupeol (Ames, Halsall, and Jones, *J.*, 1951, 450; Halsall, Jones, and Meakins, *loc. cit.*). In turn betulin and betulinic acid (Davy, Halsall, and Jones, *J.*, 1951, 2696) must be (IV; R = H, R′ = $CH_2$·OH) and (IV; R = H, R′ = $CO_2H$) in which the *iso*propenyl group is *trans* to both the hydroxymethyl and the carboxyl group.

Ruzicka and Rey (*Helv. Chim. Acta*, 1943, **26**, 2143) studied the degradation of the *iso*propenyl group of betulinic acid to a carboxyl group (·CMe:$CH_2$ ⟶ ·$CO_2H$) and isolated the resulting dicarboxylic acid. One route to the acid involved oxidation of the *iso*propenyl group of acetylbetulinic acid (IV; R = Ac, R′ = $CO_2H$) with selenium dioxide, followed by vigorous chromic acid oxidation of the resulting aldehyde (V). In

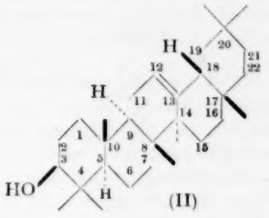
* Part XIX, preceding paper.

† With the agreement of Professor L. Ruzicka and of British triterpene chemists, the numbering of rings A and B of the pentacyclic triterpenes is to be the same as that of rings A and B of the steroids [cf. (II)].

addition to the dicarboxylic acid, a $C_{28}$-anhydride was obtained which must be (VI), in which the two carbonyl groups are *cis* to one another. An alternative structure for the anhydride involving inversion of the $C_{(17)}$ carboxyl group is extremely unlikely. It was originally concluded, on the basis of this evidence, that the *iso*propenyl group of lupeol was *cis* to the $C_{(17)}$ methyl group (Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233), but this conclusion had to be abandoned after consideration of the mechanism of the




(I)

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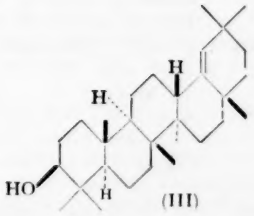


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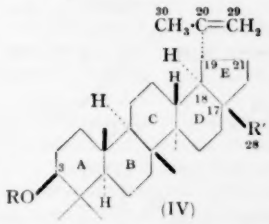
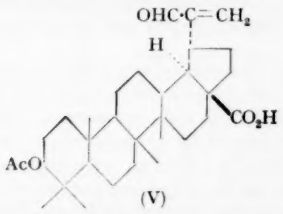



(IV)

dehydrochlorination of lupeol hydrochloride (19α-chloro-18α-oleanan-3β-ol) (Halsall, Jones, and Meakins, *loc. cit.*). Since inversion at $C_{(17)}$ is excluded, the *cis*-relationship can only arise by an inversion at $C_{(19)}$ at some stage during the oxidation of the *iso*propenyl group and the formation of the anhydride. The investigations now reported have confirmed this view and the step at which inversion occurs has been elucidated.

The naming of the compounds arising from the degradation of the *iso*propenyl group is based on the $C_{27}$-hydrocarbon (VII), trisnorlupane, and such systematic names are used in the Experimental section.

Betulin diacetate was oxidised with selenium dioxide to the αβ-unsaturated aldehyde, 3β : 28-diacetoxylup-20(29)-en-30-al, ozonolysis of which gave the bisnor-acid (VIII).

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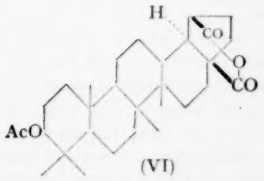
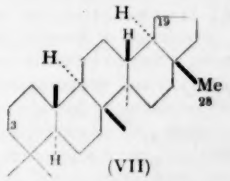



(VI)

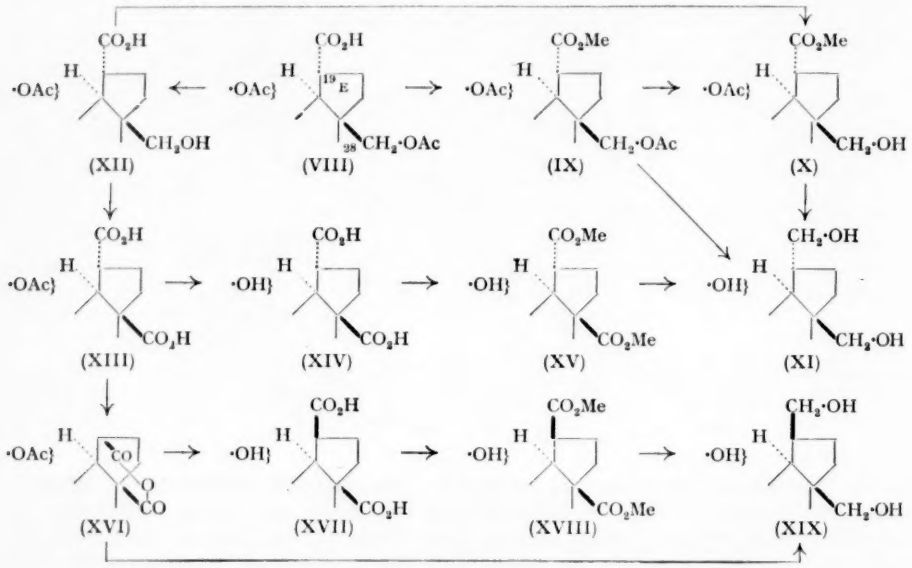



(VII)

The acid was characterised as its methyl ester (IX), partial hydrolysis of which with alkali gave the 3β-monoacetate (X). Reduction of the methyl esters (IX) and (X) with lithium aluminium hydride led to the triol (XI). Partial hydrolysis of the crude diacetoxy-acid (VIII) gave rise, in good yield, to the 3β-monoacetate (XII), oxidation of which gave the dicarboxylic acid (XIII). Compound (XIII) was hydrolysed to (XIV) which was converted into the dimethyl ester (XV) and then reduced to the triol (XI).

When compound (XIII) was heated under reflux in acetic anhydride in an attempt to convert it into an anhydride it was recovered unchanged. The anhydride (VI ≡ XVI) was only obtained when compound (XIII) was heated under reflux in acetic anhydride in the presence of toluene-*p*-sulphonic acid. This result suggested that inversion at $C_{(19)}$ occurred at this stage, being catalysed by the acidic reagent. Evidence in support of the

view that inversion occurs during the anhydride formation is provided by hydrolysis of the anhydride to the hydroxy-dicarboxylic acid (XVII) which was characterised as its dimethyl ester (XVIII). This was not identical with the dimethyl ester (XV) derived from the precursor of the anhydride. Reduction of the ester (XVIII) with lithium aluminium hydride gave the triol (XIX) which was also obtained by direct reduction of the anhydride.




The group next to the brace (·OAc}, ·OH}) represents the 3β-substituent.

This triol was different from the triol (XI). From these results it is clear that inversion at $C_{(19)}$ does not occur during the degradation of the *iso*propenyl side chain or before the anhydride formation.

## Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform, unless otherwise stated. The alumina used for chromatography had an activity of I–II unless otherwise indicated.

*Oxidation of Betulin Diacetate with Selenium Dioxide.*—Betulin diacetate (10 g.) was heated under reflux in benzene–acetic acid (400 c.c.; 1 : 3) for 2 hr. with selenium dioxide (3 g.). After filtration and evaporation the residue was dissolved in ether, and the solution was washed with 20% sodium hydroxide solution and water. The solid (10 g.) obtained by evaporation of the solution was adsorbed from benzene on deactivated alumina (300 g.). Elution with benzene (900 c.c.) gave a fraction (6 g.) which was decolorised with charcoal in ethyl acetate solution and then crystallised from ethyl acetate–ethanol, giving 3β : 28-*diacetoxylup*-20(29)-*en*-30-*al* (V; $CH_2$·OAc in place of $CO_2H$) as fine needles (4·5 g.), m. p. 237—240°, raised by further recrystallisation from acetone to 239—241°, $[\alpha]_D$ +9° (*c*, 1·8) (Found: C, 75·2; H, 9·8. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·65%). Light absorption in ethanol: Max., 2250 Å; $\varepsilon = 7000$.

*Ozonolysis of* 3β : 28-*Diacetoxylup*-20(28)-*en*-30-*al*.—The aldehyde (4 g.) in glacial acetic acid (250 c.c.) was treated with a stream of ozonised oxygen for 4 hr. The solution was diluted with water and evaporated to dryness under reduced pressure, and the residue was dissolved in ether. The acidic fraction (3·25 g.) was isolated by extraction with sodium hydroxide solution.

The crude acid (3β : 28-diacetoxytrisnorlupane-19α-carboxylic acid; VIII) (1 g.) in acetone (25 c.c.) was treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (50 g.). Elution with benzene–ether (19 : 1) (200 c.c.) gave 3β : 28-*diacetoxy*-19α-*methoxycarbonyltrisnorlupane* (IX) (400 mg.) which crystallised from methanol as needles, m. p. 161—164°, $[\alpha]_D$ −15·5° (*c*, 0·96) (Found: C, 73·0; H, 9·65. $C_{33}H_{52}O_6$ requires

C, 72·9; H, 9·6%). Elution with benzene–ether (1 : 1) (200 c.c.) gave a fraction (200 mg.) which crystallised from chloroform–methanol as prisms, m. p. 265—275°. It was probably 3β-acetoxy-28-hydroxy-19α-methoxycarbonyltrisnorlupane (see below).

*Partial Hydrolysis of* 3β : 28-*Diacetoxy*-19α-*methoxycarbonyltrisnorlupane*.—The ester (400 mg.) in methanol (25 c.c.) was treated at 20° with potassium hydroxide (45 mg.; 1·05 mol.) for 16 hr. The solution was neutralised with dilute sulphuric acid and then evaporated to half volume; crystallisation then occurred. After separation the crystals were recrystallised several times from chloroform–methanol, to give 3β-*acetoxy*-28-*hydroxy*-19α-*methoxycarbonyltrisnorlupane* (X) as prisms, m. p. 270—275°, $[\alpha]_D$ −14° (*c*, 1·12) (Found: C, 74·0; H, 10·1. $C_{31}H_{50}O_5$ requires C, 74·0; H, 10·0%).

*Reduction of* 3β : 28-*Diacetoxy*-19α-*methoxycarbonyltrisnorlupane*.—The ester (140 mg.) in anhydrous ether (20 c.c.) was refluxed for 3 hr. with a solution of lithium aluminium hydride in ether (14 c.c.; 0·5M). Excess of reagent was destroyed, and the complex decomposed, with dilute sulphuric acid. The product (100 mg.) obtained by ether-extraction crystallised from aqueous methanol as needles, m. p. 254—257°. Further recrystallisations from methanol gave 3β : 28-*dihydroxy*-19α-*hydroxymethyltrisnorlupane* (XI) as needles, m. p. 258—261°, $[\alpha]_D$ −23° (*c*, 0·86 in pyridine) (Found: C, 77·4; H, 11·3. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). The triol (210 mg.) was acetylated in pyridine (10 c.c.) with acetic anhydride (20 c.c) at 100° for 1 hr., to give 3β : 28-*diacetoxy*-19α-*acetoxymethyltrisnorlupane*, which crystallised from methanol as needles, m. p. 162—164°, $[\alpha]_D$ −21° (*c*, 1·17) (Found: C, 73·0; H, 9·85. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·75%).

*Partial Hydrolysis of* 3β : 28-*Diacetoxy*-19α-*carboxytrisnorlupane*.—The crude acid (2·5 g.) in ether (100 c.c.) was shaken with sodium hydroxide solution (100 c.c., 10%) for 1 hr. The aqueous layer was acidified and extracted with ether. The residue from the extract crystallised from methanol, to give 3β-*acetoxy*-19α-*carboxy*-28-*hydroxytrisnorlupane* (XII) as needles (2 g.), m. p. 280—295°, raised by further recrystallisation from chloroform–methanol to 300—303°, $[\alpha]_D$ −23° (*c*, 0·72) (Found: C, 73·35; H, 9·85. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%). This acid was esterified with diazomethane to give the methyl ester (X) previously described.

*Oxidation of* 3β-*Acetoxy*-19α-*carboxy*-28-*hydroxytrisnorlupane*.—The acid (1·5 g.) in acetic acid (20 c.c.) was kept at 90° for 15 min. with chromic acid solution (2 c.c.; 8N). The mixture was then diluted with water and extracted with ether. From the ethereal solution the acidic fraction was isolated by extraction with sodium hydroxide solution. The crude product (3β-acetoxy-19α-carboxytrisnorlupan-28-oic acid; XIII) was used without further purification.

*Hydrolysis of* 3β-*Acetoxy*-19α-*carboxytrisnorlupan*-28-*oic Acid*.—The acid (500 mg.) in dioxan (25 c.c.) was heated under reflux with 10% methanolic potassium hydroxide (25 c.c.) for 2 hr. The mixture was acidified and extracted with ether, and the acid obtained by sodium hydroxide extraction of the ethereal solution. The crude acid (19α-carboxy-3β-hydroxytrisnorlupan-28-oic acid; XIV) was dissolved in acetone (20 c.c.) and treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (20 g.) and eluted with benzene–ether (1 : 1) (200 c.c.), to give methyl 3β-hydroxy-19α-methoxycarbonyltrisnorlupan-28-oate (XV) which crystallised from methanol as needles (200 mg.), m. p. 210—212°, $[\alpha]_D$ −26° (*c*, 1·08) (Found: C, 73·6; H, 9·9. Calc. for $C_{30}H_{48}O_5$: C, 73·7; H, 9·9%). Ruzicka and Rey (*loc. cit.*) give m. p. 210°, $[\alpha]_D$ −13°.

*Anhydride Formation*.—3β-Acetoxy-19α-carboxytrisnorlupan-28-oic acid (2·2 g.) in acetic anhydride (130 c.c.) was heated under reflux with toluene-*p*-sulphonic acid (200 mg.) for 8 hr. The mixture was poured into water and extracted with ether. After being washed with sodium hydroxide solution and water, the ethereal extract was evaporated to give a solid (1·1 g.) which was crystallised from methanol, and from methanol–chloroform, to give the anhydride (XVI) of 3β-acetoxy-19β-carboxytrisnorlupan-28-oic acid as needles (1·0 g.), m. p. 345—350° (in sealed tube), $[\alpha]_D$ +36° (*c*, 1·19). Ruzicka and Rey (*loc. cit.*) give m. p. 352°, $[\alpha]_D$ +32°.

*Attempted Anhydride Formation*.—3β-Acetoxy-19α-carboxytrisnorlupan-28-oic acid (1·2 g.) was heated under reflux in acetic anhydride for 6 hr. The mixture was then diluted with water and extracted with ether. After removal of the acidic fraction (1·1 g.) by extraction with sodium hydroxide solution, evaporation of the ethereal extract yielded only a small amount of neutral material as a yellow gum (50 mg.) which could not be crystallised.

*Hydrolysis of the Anhydride*.—The anhydride (550 mg.) in dioxan (25 c.c.) was heated under reflux with 10% methanolic potassium hydroxide for 2 hr. The mixture was acidified, diluted with water, and extracted with ether. The extract was separated into an acidic fraction (275 mg.) and a neutral fraction (50 mg.). The latter after acetylation with acetic anhydride and pyridine yielded starting material. The acidic fraction was crystallised several times from

acetone, to give 19β-*carboxy*-3β-*hydroxytrisnorlupan*-28-*oic acid* (XVII) as needles, m. p. above 350°, $[\alpha]_D$ +63° (*c*, 0·93) (Found: C, 73·25; H, 9·65. $C_{28}H_{44}O_5$ requires C, 73·5; H, 9·65%).

The acid (250 mg.) in acetone was treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (10 g.) and eluted with benzene–ether (9 : 1) (200 c.c.) to give *methyl* 3β-*hydroxy*-19β-*methoxycarbonyltrisnorlupan*-28-*oate* (XVIII) as needles (from methanol), m. p. 208—210°, $[\alpha]_D$ +69° (*c*, 0·97) (Found: C, 73·55; H, 9·95. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

*Reduction of Methyl* 3β-*Hydroxy*-19β-*methoxycarbonyltrisnorlupan*-28-*oate* (XVIII).—The ester (275 mg.) in anhydrous ether (100 c.c.) was heated under reflux with lithium aluminium hydride (200 mg.) for 3 hr. Excess of reagent was destroyed with water, and the complex was decomposed with dilute sulphuric acid. Ether-extraction yielded 3β : 28-dihydroxy-19β-hydroxymethyltrisnorlupane (XIX) (220 mg.), which was crystallised three times from methanol as needles, m. p. 265—270°, $[\alpha]_D$ +39° (*c*, 0·64 in pyridine).

*Reduction of the Anhydride* (XVI).—The anhydride (90 mg.) was dissolved in di-*n*-butyl ether (30 c.c.), and an ethereal solution of lithium aluminium hydride (0·5M; 15 c.c.) was added. The diethyl ether was distilled off and then the remaining solution was heated under reflux for 3 hr. The mixture was then worked up as described above, yielding 3β : 28-dihydroxy-19β-hydroxymethyltrisnorlupane (50 mg.) which crystallised from methanol as needles, m. p. 265—270°, undepressed on admixture with the triol prepared from methyl 3β-hydroxy-19β-methoxycarbonyltrisnorlupan-28-oate (XVIII).

*Reduction of Methyl* 3β-*Hydroxy*-19α-*methoxycarbonyltrisnorlupan*-28-*oate* (XV).—The ester n anhydrous ether (25 c.c.) was heated under reflux with ethereal lithium aluminium hydride (0·5M; 10 c.c.) for 3 hr. The mixture was worked up in a similar manner to that in previous experiments. The product (100 mg.) which crystallised from methanol as needles, m. p. 255—259°, $[\alpha]_D$ −22° (*c*, 0·78 in pyridine), was identical with 3β : 28-dihydroxy-19α-hydroxymethyltrisnorlupane (XI) prepared from (IX).

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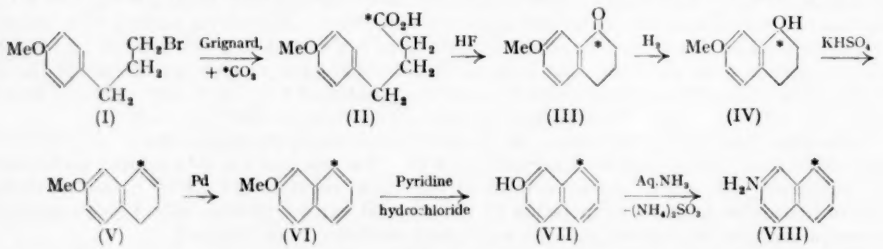
## 601. *Synthesis of* 2-[8-$^{14}$C]*Naphthylamine.*

By J. R. CATCH, H. P. W. HUGGILL, and A. R. SOMERVILLE.

2-Naphthylamine labelled with $^{14}$C in position 8 has been synthesized with a specific activity of about 2·5 mc./millimole. [1-$^{14}$C]Naphthalene is produced as a by-product.

2-NAPHTHYLAMINE labelled with $^{14}$C was required for an investigation of its mode of action as a bladder carcinogen. It was synthesized by the reactions formulated.

Direct reduction of (III) to the tetralin was slow and uncertain and dehydrogenation




of the latter produced up to 40% of naphthalene as well as (VI). It was more satisfactory to proceed by way of (IV) and (V) as shown though the hydrogenation was still erratic and was not improved by recrystallizing the tetralone. The product from dehydrogenation of (V) was distilled, to give a mixture of naphthalene and (VI), which was treated with

pyridine hydrochloride to hydrolyse the methoxy-compound to the naphthol, which was then extracted with alkali.

The naphthylamine was purified by repeated sublimation from silica, a method developed for larger-scale work by Dr. R. A. M. Case and shown by him to produce very pure material from commercial naphthylamine (personal communication). The purified naphthylamine is sensitive to light and oxygen, but in their absence has been kept unchanged for 18 months.

Animal experiments with 2-[8-$^{14}$C]naphthylamine will be reported elsewhere.

## Experimental

3-p-*Methoxyphenylpropyl Bromide.*—(*a*) Ethyl *p*-methoxycinnamate was prepared from anisaldehyde and ethyl acetate in ether in the presence of sodium as described by Horeau (*Bull. Soc. chim.*, 1948, **15**, 414) except that the sodium was powdered by stirring it under toluene, excess of toluene being removed by decantation. Yields of 73% on anisaldehyde were obtained. The ethyl *p*-methoxycinnamate had b. p. 184—187°/16 mm.

(*b*) Ethyl *p*-methoxycinnamate (226 g.) in ethanol (1 l.) was shaken with hydrogen at room temperature and atmospheric pressure in presence of palladized barium sulphate (2%; 1 g.). Reduction was complete (absorption, 25 l.) in about 16 hr., three further additions of catalyst being necessary. Filtration, evaporation, and distillation under reduced pressure gave ethyl β-*p*-methoxyphenylpropionate (218 g., 95%), b. p. 160—168°/18 mm.

No hydrogenation took place over a catalyst of (not recently prepared) Raney nickel.

(*c*) Ethyl β-*p*-methoxyphenylpropionate (218 g.) in ether was added with stirring to lithium aluminium hydride (25 g.) in boiling ether, excess of hydride decomposed by ethyl acetate, water and dilute hydrochloric acid were added, and the ethereal layer was dried and evaporated. Distillation of the residue gave 3-*p*-methoxyphenylpropan-1-ol (152 g., 87%), b. p. 164—168°/18 mm., which largely crystallized at room temperature (lit., m. p. 26°).

Direct reduction of ethyl *p*-methoxycinnamate with lithium aluminium hydride under similar conditions gave only 3-*p*-methoxyphenylprop-2-en-1-ol in 37% yield. The reduction with sodium in amyl alcohol used by Horeau was found to be very sensitive to traces of water and the above two-stage method gave better yields.

(*d*) 3-*p*-Methoxyphenylpropyl bromide was prepared in 67% yield as described by Horeau (*loc. cit.*) from the alcohol and phosphorus tribromide in carbon tetrachloride at 60—70°. Increasing the proportion of phosphorus tribromide or the reaction time did not improve the yield. The compound did not interact with magnesium in ether alone, but after initiation with methyl iodide a moderate reaction took place. For purification the bromide (81 g.) was distilled through a 4″ column packed with glass rings, to give fractions: (1) b. p. 150—163°/22 mm. (1 g.), 97% pure on bromine content, somewhat discoloured; (2) b. p. 163—166°/22 mm. (66 g.), 100% pure, colourless; (3) residue (12 g.), 93% pure on bromine content.

A " tracer " run with $^{14}CO_2$ of low activity was now carried out as follows:

4-p-*Methoxyphenylbutan*[$^{14}$C]*oic Acid.*—3-*p*-Methoxyphenylpropyl bromide (900 mg.), magnesium turnings (110 mg.), and a crystal of iodine were refluxed in dry ether (5 c.c.) for 1 hr. The Grignard solution thus obtained was frozen in liquid nitrogen, the flask connected to a vacuum system and evacuated, and $^{14}CO_2$ (2·65 millimoles, 38,000 c.p.m./millimole) condensed into it. After warming to room temperature and storage for 1½ hr. with occasional shaking, the mixture was decomposed with ice and dilute sulphuric acid in a separating funnel (fitted with mechanical stirring), and the acid extracted from the ethereal layer with sodium carbonate solution. After being washed with ether, the sodium carbonate solution was acidified and extracted with ether, and the acid obtained by evaporating this ethereal extract was sufficiently pure for the next stage. The yield was 493 mg. (95%). In larger runs of 13—14 millimoles the yields were 90—91%.

7-*Methoxy*-1-[1-$^{14}$C]*tetralone* (cf. Campbell and Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 934).—The ethereal solution of β-*p*-methoxyphenylbutanoic acid obtained above was evaporated in a " Polythene " tube, and the residue dissolved in anhydrous hydrogen fluoride (*ca.* 5 c.c.) and kept overnight in the stoppered tube. Most of the hydrogen fluoride was then allowed to evaporate, and the remainder neutralized with solid sodium carbonate. The ketone was extracted with ether and washed with sodium carbonate solution. Evaporation of the ether gave yellow crystals (403 mg., 90%) which were dissolved in ethereal diazomethane and set aside for a few min. to methylate any free phenol. The solution was evaporated and the residue used directly for the next stage.

*2-Methoxy[8-$^{14}$C]naphthalene.*—7-Methoxytetralone was hydrogenated in methanol over palladium black (50 mg.) with magnetic stirring. Uptake was very slow, and addition of fresh catalyst was often necessary. After the uptake of about 1 mol. of hydrogen, the solution was filtered and evaporated, and the residue heated with freshly fused potassium hydrogen sulphate (300 mg.) at 200° for 2 hr. The melt was then extracted with ether, which was washed with water, dried, and evaporated, and fresh palladium black (50 mg.) was added to the residue. A deep blue colour was immediately produced, which however disappeared at 200—230°. After 2½ hr. at this temperature the residue was distilled at *ca.* 60°/$10^{-2}$ mm. The distillate (288 mg.) solidified incompletely, probably owing to the presence of naphthalene, which was not separated at this stage.

*2-[8-$^{14}$C]Naphthylamine.*—The distillate obtained above was heated with 10 times its weight of pyridine hydrochloride (commercial, containing some pyridine which is desirable for washing sublimed material out of the condenser) at 200° for 6 hr. (cf. Prey, *Ber.*, 1941, **74**, 1219). The melt was taken up in ether and washed with dilute hydrochloric acid, and the naphthol extracted with sodium hydroxide solution, giving 135 mg. of alkali-soluble material; 137 mg. were recovered from the ether, and naphthalene was isolated therefrom by sublimation (m. p. 76—79°; picrate, m. p. 149—150°). Further purification by chromatography on alumina and recrystallization from alcohol gave material of m. p. 79·5°.

The crude naphthol was transferred to a " Pyrex " tube (*ca.* 20 × 200 mm.), which was then half filled with a mixture of equal parts of aqueous ammonia (*d* 0·880) and freshly prepared ammonium sulphite solution, sealed, and heated at 150° for 17 hr. On cooling, the mixture was extracted with ether, which was washed with water and extracted with dilute hydrochloric acid, to afford the naphthylamine (101 mg., crude; 26·5% from $^{14}CO_2$).

In the high-activity run, 27·2 millimoles of $^{14}CO_2$ (2·51 mc./millimole) were used. 3·24 millimoles (13%) of the acid (II) were recovered from the hydrogen fluoride cyclization, and 1·37 millimoles (5%) of 2-naphthol were removed for purification. The yield of naphthylamine was 4·4 (16%) and of naphthalene 1·52 millimoles (5·6%).

For radioactive assay the products were diluted with pure carrier material. The naphthol and naphthylamine were also converted into their acetyl derivatives which were purified and assayed similarly. All measurements were by combustion in the dry way and end-window counting of infinitely thick films in standard geometry. The values, calculated to the provisional standard of the National Bureau of Standards, were as follows (mc./millimole): 2-naphthol (crude) 2·44; 2-naphthyl acetate (pure) 2·40; 2-naphthylamine (crude) 2·52; acetonaphthylamide (pure) 2·48; naphthalene, crude 2·51, pure 2·69.

The naphthylamine (after purification by the method described below) was also assayed by a gas counting method. Three samples of the amine were burnt in a standard microanalytical combustion tube and the gases collected by freezing in liquid nitrogen. The carbon dioxide was then freed from water by evaporation from a solid carbon dioxide–acetone bath, and after dilution with inactive carbon dioxide an aliquot was counted in a $CO_2$–$CS_2$ gas counting tube (cf. A. F. Henson, *Brit. J. Appl. Phys.*, 1953, **4**, 217). The values obtained were: $2{\cdot}988 \times 10^7$, $3{\cdot}028 \times 10^7$, $2{\cdot}937 \times 10^7$ c.p.m./mg. (mean $2{\cdot}984 \pm 0{\cdot}027 \times 10^7$). The efficiency of the counters (72%) was measured by oxidizing samples of standard labelled " Perspex " and counting the carbon dioxide formed. This correction being made, the specific activity of the naphthylamine is 2·67 mc./millimole.

*Purification of 2-[8-$^{14}$C]Naphthylamine.*—Naphthylamine and 10% (wt.) of silica (100—200 mesh) were introduced into a long tube having several constrictions. The amine was sublimed (80—95°/$10^{-6}$ mm.) beyond the first constriction, which was sealed off, and the amine sublimed twice more to ensure the removal of silica. The product still had a faint creamy tinge, so the process was repeated, yielding a pure white compound, m. p. 108·4—109·9°.

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## 602. *Experiments on the Synthesis of Mycolipenic Acid. Part I.*

By A. S. Bailey, N. Polgar, and Sir Robert Robinson.

The structure advanced for mycolipenic acid (Polgar and Robinson, *Chem. and Ind.*, 1951, 685) has been confirmed in respect of the length of the normal chain.

The synthesis of the optically inactive acid (or of a stereoisomeride) is now described.

Mycolipenic acid * is a dextrorotatory acid from the lipids of tubercle bacilli which has already been shown to have the structure (I), where *n* was stated to be probably 17 (Polgar and Robinson, *Chem. and Ind.*, 1951, 685). The stepwise degradations of mycolipenic acid already reported resulted in the isolation of a straight-chain methyl ketone which gave a semicarbazone of m. p. 124·5° (the m. p. 122°, given in the earlier communication rose on further crystallisations). The melting point of this semicarbazone was not depressed on admixture with *n*-eicosan-2-one semicarbazone, m. p. 126—126·5°, or *n*-nonadecan-2-one semicarbazone, m. p. 125·5—126°. The absence of depression of melting points on admixture does not provide sufficient proof of identity in this series, and we are greatly indebted to Mrs. D. M. Crowfoot Hodgkin for identifying the degradation product as *n*-eicosan-2-one by comparing the *X*-ray diffraction powder photographs of the above semicarbazones. Mrs. Hodgkin reported as follows:

"A specimen of the semicarbazone of the degradation product was compared with specimens of the semicarbazones of eicosan-2-one and nonadecan-2-one. All three crystallised in very similar small plates which were hardly distinguishable by measurement under the microscope. Powder photographs, taken with a 3-cm. camera, showed that the derivative of the degradation product could be identified with that of eicosan-2-one. The spacings of the lines observed for these two specimens (cf. Table) were all identical within the limits of experimental error and a few small differences in the appearance of the lines could be accounted for by different degrees of orientation of the fragments in the specimens used for photography. The photograph of the semicarbazone of nonadecan-2-one, although very similar in general appearance, differed in the spacings of many of the weaker lines. The identity of the longer spacings of the semicarbazone of eicosan-2-one and that of the degradation product were further checked by photographs on plates at greater crystal-to-film distances."

*Principal wide-angle lines on powder photographs.*

| Semicarbazone of nonadecan-2-one | | Semicarbazone of the degradation product | | Semicarbazone of eicosan-2-one | |
|---|---|---|---|---|---|
| Spacing | Intensity | Spacing | Intensity | Spacing | Intensity |
| 6·05 | w | 6·34 | w | 6·40 | w |
| 5·59 | w + | 4·43 | m | 4·42 | m |
| 5·02 | w + | 4·08 | vw | 4·09 | vw |
| 4·60 | m | 3·90 | w + | 3·90 | w |
| 4·38 | w | 3·73 | s | 3·72 | s |
| 3·71 | s | 3·44 | w | 3·55 | ?vw |
| 2·21 | w | 2·44 | w | 2·46 | w |
| 2·12 | w | 2·40 | w | 2·40 | w |
| | | 2·14 | vw | 2·14 | Blurred |
| | | 2·12 | w | | w Blurred |

The provisional formulation of the degradation product as eicosan-2-one (Polgar and Robinson, *loc. cit.*) is thus confirmed. It follows that in formula (I) *n* is 17, *i.e.*, mycolipenic acid is 2 : 4 : 6-trimethyltetracos-2-enoic acid.

At this point the opportunity is taken to comment briefly on "phthioic acid," obtained by Spielman and Anderson (*J. Biol. Chem.*, 1935—36, **112**, 759) from the lipids of human tubercle bacilli. This acid, formulated by them as $C_{26}H_{52}O_2$, was isolated by a procedure

* The suffix I is now omitted because there is no evidence of the natural occurrence of a second, closely related, unsaturated isomeric acid.

involving hydrogenation, but the value given for its specific rotation (+12·5°) suggests that the hydrogenation was incomplete (cf. Chanley and Polgar, *Nature*, **1950**, **166**, 693). It is doubtless partly due to this partial hydrogenation that Cason and Sumrell (*J. Biol. Chem.*, 1951, **192**, 405), on fractionation of the methyl esters of " phthioic acid " originating from the work of Anderson and his collaborators, obtained a variety of products. These were claimed to comprise at least twelve components, including αβ-unsaturated dextro- and lævo-rotatory acids.

Whilst awaiting with interest the more precise elaboration of these findings we can say at once that they do not accord with the impressions gained from investigations made in these laboratories.

In regard to the dextrorotatory acid which the American authors termed $C_{27}$-phthienoic acid, it should be noted that Cason, Freeman, and Sumrell (*ibid.*, p. 415) have provided no evidence of its structure by degradation, nor any clear proof of the presence of methyl substituents. The physical methods employed led these authors to assign a methyl group to $C_{(5)}$. Freeman (*J. Amer. Chem. Soc.*, 1953, **75**, 1859), ignoring our disclosure of the full constitution of mycolipenic acid in 1951, has now found by comparison of infra-red spectra that one methyl branch is on $C_{(4)}$.

There can be very little doubt but that $C_{27}$-phthienoic acid and mycolipenic acid are identical.

The molecule of mycolipenic acid contains two asymmetric carbon atoms and the acid is therefore one of four possible optically active forms. The acid is dextrorotatory, and the same applies to the α-methyl-substituted acids obtained as degradation products (Polgar and Robinson, *loc. cit.*) of which the α-carbon atom corresponds to $C_{(4)}$ and $C_{(6)}$, respectively, of mycolipenic acid. These considerations will be helpful in synthesising optically active intermediates corresponding in configuration to the natural product. Experiments in this direction are in progress. Meanwhile, in the present communication a synthesis of the optically inactive acids is placed on record.

The starting point was 2-methyleicosanoic acid (II), obtained by a malonic ester synthesis employing octadecyl iodide and ethyl methylmalonate. Reduction of (II) with lithium aluminium hydride afforded 2-methyleicosan-1-ol. The latter was converted into the iodide which by condensation with ethyl methylmalonate and the usual subsequent procedure gave 2 : 4-dimethyldocosanoic acid (III). This was transformed by repetition of the above processes into 2 : 4-dimethyldocosan-1-ol, and 2 : 4 : 6-trimethyltetracosanoic acid (IV). Bromination of the acid (Hell–Volhard–Zelinsky method), followed by reaction of the α-bromo-acid bromide with methanol and dehydrobromination of the resulting bromo-ester by means of pyridine, and hydrolysis of the product, gave 2 : 4 : 6-trimethyltetracos-2-enoic acid (I; $n = 17$).

(I) $CH_3 \cdot [CH_2]_n \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH{:}CMe \cdot CO_2H$ $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CO_2H$ (II)
(III) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ (IV)

In earlier experiments preparation of 2 : 4-dimethyldocosanoic acid (III) was attempted by a shorter route, namely, by oxidation of the appropriate alkyl-substituted *tert.-cyclo*hexanol (cf. Fieser and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1948, **70**, 3352). For this purpose, 3 : 5-dimethyl-1-*n*-octadecyl*cyclo*hexan-1-ol was prepared by a Grignard reaction between *n*-octadecyl bromide and 3 : 5-dimethyl*cyclo*hexanone, obtained by hydrogenation of 1 : 3 : 5-xylenol, and oxidation of the resulting alcohol to the ketone. Oxidation of the product with chromic acid was expected to yield 2 : 4-dimethyl-6-oxodocosanoic acid; however, only small quantities of acidic material were obtained and this approach was not pursued further.

The physiological properties of 2 : 4 : 6-trimethyltetracos-2-enoic acid and related acids have been examined by Dr. J. Ungar of Glaxo Laboratories Ltd. The preliminary results suggest that the acid is a marked irritant which causes fibrotic changes of non-specific character in the organs of the peritoneal cavity. On the other hand, 2 : 4-dimethyldocosanoic acid (III), obtained as an intermediate in the above synthesis, exhibited a moderate specific activity similar to that seen previously with 3 : 12 : 15-trimethyldocosanoic acid. It produced multiple white nodules of cheesy appearance on the organs

within the peritoneal cavity and on the diaphragm; in particular, the spleen and omentum showed multiple granulomatous lesions with central necrosis. 2 : 4-Dimethyldocos-2-enoic acid (forthcoming publication) showed only very low activity of a non-specific character, and it thus appears that the introduction of an $\alpha\beta$-double bond decreases the activity.

## Experimental

*Nonadecan-2-one.*—Hexadecyl iodide (3 g.; prepared from hexadecan-1-ol by interaction with iodine and red phosphorus) was added to ethyl sodioacetoacetate [from sodium (0·2 g.), ethanol (10 c.c.), and ethyl acetoacetate (2 c.c.)], and the mixture refluxed for 4 hr. Next day potassium hydroxide (2·5 g.) in water (30 c.c.) was added, and the mixture kept for 1 hr. with frequent shaking. The resulting solution was then refluxed with 5N-hydrochloric acid (20 c.c.) for 2 hr. The product was collected with ether, and the ethereal solution washed successively with 5% aqueous potassium hydroxide, and water, and dried ($Na_2SO_4$). Evaporation then gave the crude *ketone* (2·4 g.) which, after crystallisation from ethanol, had m. p. 53·5° (Found: C, 81·1; H, 13·5. $C_{19}H_{38}O$ requires C, 80·9; H, 13·5%). Its *semicarbazone* had m. p. 125·5—126° after crystallisation from ethanol (Found: C, 71·0; H, 12·2; N, 12·5. $C_{20}H_{41}ON_3$ requires C, 70·8; H, 12·1; N, 12·4%).

n-*Eicosan-2-one.*—This ketone was prepared according to the procedure of Churchward, Gibson, Meakins, and Mulley (*J.*, 1950, 959). Its semicarbazone had m. p. 126—126·5° after crystallisation from ethanol (Found: C, 71·1; H, 12·2. Calc. for $C_{21}H_{43}ON_3$: C, 71·4; H, 12·2%).

2-*Methyleicosanoic Acid* (II).—Iodine (32 g.) was added in small portions during 1 hr. to a mixture of octadecan-1-ol (61 g.) and red phosphorus (2·6 g.) at 130—140° (bath). The temperature was then raised to 170—180° and the heating continued for another 3 hr. After cooling, the product was taken up in ether, and the ethereal solution filtered through glass wool. It was then washed, successively, with water, aqueous sodium hydrogen sulphite, and water, dried ($MgSO_4$), and distilled, affording octadecyl iodide, b. p. 156—160°/0·1 mm. This (134 g.) was added with stirring during 10 min. to the sodio-derivative of ethyl methylmalonate, obtained from sodium (12·3 g.), *n*-butanol (200 c.c.; dried over $K_2CO_3$ and distilled), and ethyl methylmalonate (92 g.; Blatt, *Org. Synth.*, Coll. Vol. II, 1943, pp. 272, 279), and the mixture was refluxed for 7 hr. Next day potassium hydroxide (60 g.) in water (75 c.c.) was added, and the mixture refluxed with stirring for 10 hr. The butanol was then removed by distillation, water being added at the same rate as the butanol distilled. When most of the butanol had been removed, the liquid frothed considerably. Excess of hydrochloric acid was added at this stage, and the distillation continued for another hour, to remove the remaining butanol. When the mixture was cooled the crude substituted malonic acid solidified. It was collected, washed with a little ether, dried, and then decarboxylated at 160—170° (bath) under reduced pressure for 3 hr. The product was taken up in benzene, and the solution filtered. Removal of the solvent and crystallisation of the residual product from light petroleum (b. p. 60—80°) afforded 2-methyleicosanoic acid, m. p. 61·8—62° (95 g., 83%). Schneider and Spielman (*J. Biol. Chem.*, 1942, **142**, 345) give m. p. 61·5—62°; Stenhagen and Tagstrom (*Svensk Kem. Tidskr.*, 1942, **54**, 145; *Chem. Abs.*, 1944, **38**, 2314) give m. p. 61·7—62°. The p-*bromophenacyl* ester crystallised from ethanol in clusters of needles, m. p. 83—84° (Found: C, 67·0, 66·1; H, 9·2, 9·3. $C_{29}H_{47}O_3Br$ requires C, 66·6; H, 9·0%).

2-*Methyleicosan*-1-*ol.*—2-Methyleicosanoic acid (45 g.) was refluxed with ethanol (500 c.c.) and concentrated sulphuric acid (22 c.c.) for 6 hr. After removal of most of the ethanol by heating on a steam-bath under reduced pressure, the residual product was extracted with ether. The extract was washed with water and dried ($MgSO_4$), and the ether removed. A solution of the resulting crude ester in dry ether (100 c.c.) was then added to a suspension of lithium aluminium hydride (4 g.) in ether (350 c.c.) at such a rate that the ether refluxed steadily. After 3 hr.' refluxing the excess of lithium aluminium hydride was decomposed by the addition of ethyl acetate; water was then added, followed by the addition of dilute sulphuric acid. The aqueous layer was extracted with ether. The combined ethereal extracts were washed, successively, with dilute sulphuric acid, water, 5% aqueous potassium hydroxide (no acidic material was found in this washing), and water, and dried ($MgSO_4$). After evaporation of the ether, the residual oil (41·5 g.) solidified on cooling and had m. p. 42—44°. On crystallisation from light petroleum (b. p. 40—60°), 2-*methyleicosan*-1-*ol* was obtained as clusters of blades, m. p. 48·5—49° (Found: C, 80·2, 80·3; H, 14·0, 13·8. $C_{21}H_{44}O$ requires

C, 80·8; H, 14·1%). The *phenylurethane* crystallised from light petroleum (b. p. 40—60°) as colourless needles, m. p. 61—62° (Found: C, 78·1; H, 11·4. $C_{28}H_{49}O_2N$ requires C, 77·9; H, 11·4%).

1-*Iodo*-2-*methyleicosane*.—A mixture of 2-methyleicosan-1-ol (20 g.) and red phosphorus (0·92 g.) was heated at 120° (bath), and iodine (12·2 g.) added during 30 min. The bath-temperature was gradually raised to 160—180° during 30 min. and maintained thereat for another 3 hr. After cooling, ether was added, and the ethereal solution filtered through glass wool, then washed successively with water, aqueous sodium hydrogen sulphite, 5% aqueous potassium hydroxide, and water, and dried ($MgSO_4$). Distillation afforded 1-*iodo*-2-*methyleicosane* (22 g.), b. p. 166—170°/0·03 mm., m. p. 21—22° (thermometer in melt) (Found: C, 59·8; H, 10·2; I, 29·0. $C_{21}H_{43}I$ requires C, 59·8; H, 10·2; I, 30·0%).

2 : 4-*Dimethyldocosanoic Acid* (III).—The last mentioned iodide (40 g.) was added during 5 min. to the sodio-derivative of ethyl methylmalonate [from sodium (3·32 g.), *n*-butanol (80 c.c.), and ethyl methylmalonate (25 g.)], and the mixture refluxed for 7 hr. Next day the product was hydrolysed by refluxing it with potassium hydroxide (16 g.) in water (20 c.c.) for 7 hr., and worked up by the procedure given for a previous example except that the crude malonic acid (35·4 g.) was isolated by ether-extraction. Crystallisation of a small quantity from light petroleum (b. p. 40—60°) gave 2-*carboxy*-2 : 4-*dimethyldocosanoic acid* as clusters of fine needles, m. p. 66—68° (Found: C, 73·2; H, 11·7. $C_{25}H_{48}O_4$ requires C, 72·8; H, 11·7%). The remainder of the crude acid was decarboxylated by heating it at 160° (bath) for 2 hr. On distillation 2 : 4-*dimethyldocosanoic acid*, b. p. 190—195°/0·04 mm., m. p. 28—29°, was obtained. After resolidification, it melted at 38—41°. It crystallised from light petroleum (b. p. 40—60°) as fine needles, m. p. 50—51° (Found: C, 78·1; H, 13·3. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·1%). The p-*bromophenacyl* ester formed fine needles (from ethanol), m .p. 57—58° (Found: C, 78·1; H, 13·3. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·1%).

2 : 4-*Dimethyldocosan*-1-*ol*.—A solution of 2 : 4-dimethyldocosanoic acid (10 g.) in dry ether (100 c.c.) was added dropwise to lithium aluminium hydride (1·8 g.) in ether (100 c.c.), and the mixture refluxed for 4 hr. The product was worked up as described for a previous example. Distillation afforded 2 : 4-*dimethyldocosan*-1-*ol* (9·6 g.), b. p. 172—176°/0·1 mm., m. p. 36—39° (Found: C, 81·7; H, 13·9. $C_{24}H_{50}O$ requires C, 81·4; H, 14·1%).

2 : 4 : 6-*Trimethyltetracosanoic Acid* (IV).—Iodine (6·1 g.) was added to a mixture of the above alcohol (9·5 g.) and red phosphorus (0·45 g.), heated at 110—120° (bath), during 30 min.; the mixture was then heated at 160—180° (bath) for 3 hr., and the product worked up as described for previous examples. The resulting iodide (10 g.) had b. p. 190—200°/0·03 mm.

This iodide (9 g.) was added to the sodio-derivative of ethyl methylmalonate [from sodium (0·96 g.), *n*-butanol (20 c.c.), and ethyl methylmalonate (7 g.)], and the mixture refluxed for 7 hr. Potassium hydroxide (8 g.) in water (8 c.c.) was then added, and the mixture refluxed for 5 hr. After working up by the usual method, the crude malonic acid was collected by means of ether. Crystallisation from light petroleum (b. p. 40—60°) gave 2-*carboxy*-2 : 4 : 6-*trimethyltetracosanoic acid* as fine needles, m. p. 62—65° (Found: C, 74·5; H, 12·2. $C_{28}H_{54}O_4$ requires C, 74·1; H, 11·9%). The remainder of the crude acid was decarboxylated at 160° (bath). Distillation of the product afforded 2 : 4 : 6-*trimethyltetracosanoic acid* (5·5 g.), b. p. 210—215°/0·08 mm. (Found: C, 79·4; H, 13·1. $C_{27}H_{54}O_2$ requires C, 79·1; H, 13·2%).

2 : 4 : 6-*Trimethyltetracos*-2-*enoic Acid* (I; $n = 17$).—Trimethyltetracosanoic acid (2·1 g.) was heated with bromine (3·5 g.) in the presence of red phosphorus (0·17 g.) in a boiling water-bath for 8 hr. After cooling, dry methanol (20 c.c.) was added, and the mixture refluxed for 2 hr. Dilution with water and extraction with ether afforded the crude bromo-ester. This was refluxed with pyridine (20 c.c.) for 18 hr. After addition of dilute hydrochloric acid, the product was isolated by means of ether, and the ethereal extract washed successively with dilute hydrochloric acid and water. The ethereal solution was then evaporated, and the residual crude ester hydrolysed by refluxing it with a solution of potassium hydroxide (1 g.) in water (2 c.c.) and ethanol (8 c.c.) for 1·5 hr. Acidification of the product furnished 2 : 4 : 6-*trimethyltetracos*-2-*enoic acid* (1·2 g.), b. p. 216—218°/0·25 mm. (Found: C, 79·3; H, 12·5. $C_{27}H_{52}O_2$ requires C, 79·4; H, 12·8%). Light absorption: Max., 2140 Å; log ε, 4·12. Its *amide* had m. p. 40° after crystallisation from methanol (Found: N, 3·6. $C_{27}H_{53}ON$ requires N, 3·4%).

3 : 5-*Dimethylcyclohexanone*.—3 : 5-Dimethyl*cyclo*hexanol, prepared by hydrogenation of 1 : 3 : 5-xylenol over Raney nickel at 180°/80 atm., was oxidised by means of potassium dichromate and dilute sulphuric acid in the usual manner. 3 : 5-Dimethyl*cyclo*hexanone, b. p. 178—180°, formed a semicarbazone, m. p. 206—207°, in agreement with the records but the 2 : 4-dinitrophenylhydrazone, which crystallised from ethanol in clusters of orange-yellow rods,

had m. p. 166—167° (Birch, *J.*, 1947, 1642, reports m. p. 155—157°). The ketone can occur in stereoisomeric forms and this is a possible cause of the divergence.

3 : 5-*Dimethyl*-1-n-*octadecyl*cyclo*hexan*-1-*ol*.—3 : 5-Dimethyl*cyclo*hexanone (15·1 g.) in ether (20 c.c.) was added to an ice-cold Grignard solution from octadecyl bromide (33·3 g.; prepared by the procedure described by Blatt, *Org. Synth.*, Coll. Vol. II, 1943, p. 246, except that hydrogen bromide was passed into the reaction mixture for a total time of about 6 hr.), magnesium (2·4 g.), and ether (150 c.c.), and the mixture was refluxed for 1·5 hr. Next day, ice and aqueous ammonium chloride were added. The ethereal layer was filtered to remove hexatriacontane, washed with water, and dried ($K_2CO_3$). On distillation, the fraction of b. p. 180—210°/0·1 mm. (20·4 g.) was collected. This solidified on cooling, and had m. p. 43—45°. The *alcohol* crystallised from ethyl acetate–methanol (4 : 1) in fine needles, m. p. 50—51° (Found : C, 82·4; H, 13·6. $C_{26}H_{52}O$ requires C, 82·1; H, 13·7%). Heating it with iodine gave the corresponding *olefin*, m. p. 36—37° (Found : C, 85·9; H, 14·0. $C_{26}H_{50}$ requires C, 86·2; H, 13·8%).

Attempted oxidations of the alcohol (4-g. portions) with chromium trioxide in acetic acid, following the procedure of Fieser and Szmuszkovicz (*J. Amer. Chem. Soc.*, 1948, **70**, 3352), failed to yield any significant amounts of acidic material.

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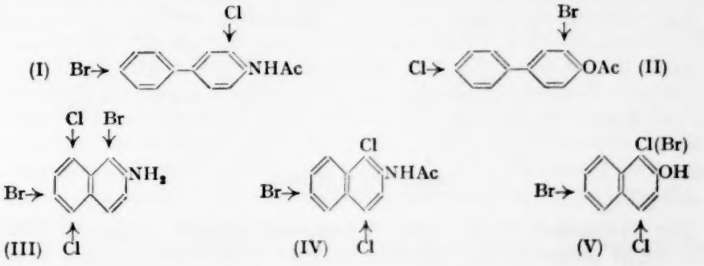
## 603. *The Halogenation of β-Naphthylamine and its Derivatives.*

By F. BELL.

A comparison has been made between the action of chlorine and of bromine on a number of 2-sulphonamidonaphthalenes, and the properties of a number of additive compounds are described.

MODERN theories of substitution tend to ignore the differences which exist between the action of chlorine and of bromine on aromatic compounds. Such differences are most clearly perceived in compounds containing more than one nucleus. Thus 4-acetamidodiphenyl (I) undergoes chlorination in position 3 but brominates mainly in position 4′ (Scarborough and Waters, *J.*, 1926, 557; Kenyon and Robinson, *J.*, 1926, 3050). On the other hand 4-acetoxydiphenyl (II) brominates in position 3 and chlorinates in position 4′, a result which indicates that mere size of the halogen atom scarcely enters into the problem (Savoy and Abernethy, *J. Amer. Chem. Soc.*, 1942, **64**, 2220, 2719). Many similar examples are found in the naphthalene series. β-Naphthylamine (III) in sulphuric acid solution chlorinates in positions 5 : 8 (Claus and Philipson, *J. pr. Chem.*, 1891, **43**, 58) but brominates in positions 1 : 6 (Claus and Jack, *J. pr. Chem.*, 1898, **57**, 1). Again, whereas 1-chloro-2-acetonaphthalide (IV) in acetic acid chlorinates in position 4 (Clemo and Legg, *J.*, 1947,

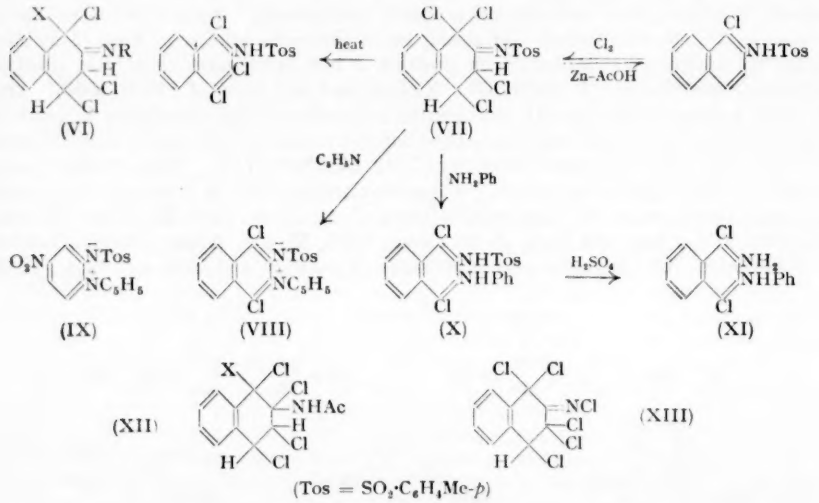



543) it brominates in position 6 (Armstrong and Rossiter, *Chem. News*, 1891, **63**, 137) and, similarly, β-naphthol (V) yields the 1 : 6-dibromo-derivative but the 1 : 4-dichloro-derivative (James and Woodcock, *J.*, 1951, 1931).

Halogenation may follow a free-radical mechanism, may involve a transition complex with positive halogen entering the nucleus, or may proceed by an addition–elimination process. The fundamental differences between chlorine and bromine which determine the relative likelihood of these routes may be modified by choice of solvent. Although the addition–elimination process of substitution is at present generally ignored or even rejected, the only positive evidence against it appears to be that in a paper by Price (*J. Amer. Chem. Soc.*, 1936, **58**, 2101) which contains a study of but one particular reaction, *viz.*, the conversion of phenanthrene into 9-bromophenanthrene. It was thought that a study of the halogenation of 2-sulphonamidonaphthalenes might throw light on these effects.

The monohalogenation of 2-toluene-*p*-sulphonamidonaphthalene to yield the 1-chloro- and 1-bromo-derivatives has already been described (Schuloff, Pollak, and Riess, *Ber.*, 1929, **62**, 1853; Bell, *J.*, 1932, 2733). The direction of further bromination of either of these compounds is determined entirely by the solvent. In acetic acid or chloroform position 6 is attacked, but in pyridine position 3. In view of the well-established normal inertness of position 3 in β-naphthylamine derivatives, this indicates that conditions are particularly favourable to bromination in pyridine solution, a point supported by the ready conversion of 2 : 4-dichlorotoluene-*p*-sulphonanilide into the 6-bromo-derivative under these conditions. It appears probable that the effectiveness of this method of bromination is, in part, due to attack by positive bromine derived from the additive compound, $C_5H_5NBr_2$ (Trowbridge and Diehl, *J. Amer. Chem. Soc.*, 1897, **19**, 567). This suggested that *N*-bromosuccinimide would be equally effective under the same conditions and such proved to be the case, 2-toluene-*p*-sulphonamidonaphthalene, for example, readily yielding the 1 : 3-dibromo-derivative.

Chlorine in pyridine solution was of no value as a chlorinating agent, probably owing to the ease with which chloropyridines are produced (Sell and Dootson, *J.*, 1898, **73**, 442; Reitzenstein and Breuning, *J. pr. Chem.*, 1911, **83**, 120). It was not possible in any example studied to convert a sulphonanilide into a chloro-derivative by means of this




(Tos = $SO_2{\cdot}C_6H_4Me$-*p*)

reagent. The favourable result with *N*-bromosuccinimide suggested that *N*-chlorosuccinimide might prove equally effective, in spite of previous negative results (Ziegler, Spath, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80). It was found that 2-toluene-*p*-sulphonamidonaphthalene in pyridine could be converted into the 1-chloro-derivative in fair yield. Further chlorination to the 1 : 3-dichloro-derivative could not be brought about, nor could 2 : 4-dichlorotoluene-*p*-sulphonanilide be converted into

the 2 : 4 : 6-trichloro-derivative. 1-Bromo-2-toluene-*p*-sulphonamidonaphthalene, however, gave a small yield of a dichloro-derivative.

The action of chlorine on acetic acid or chloroform solutions of 1-chloro(or bromo)-2-sulphonamidonaphthalenes led to the production of stable additive compounds of type (VI; X = Cl or Br, R = $SO_2Ph$, $SO_2{\cdot}C_6H_4Me$, or $SO_2{\cdot}C_6H_4{\cdot}NO_2$) which do not liberate iodine from potassium iodide. Similar additive compounds were not obtained from 1 : 3-dichloro-, 1 : 3 : 4-trichloro-, 1 : 3-dibromo-, 1-iodo-, and 1-nitro-2-toluene-*p*-sulphonamidonaphthalenes; or from 4-chloro- and 2 : 4-dichloro-1-toluene-*p*-sulphonamidonaphthalenes; or from 2 : 4-dichlorotoluene-*p*-sulphonanilide and 3 : 5-dichlorotoluene-*p*-sulphon-4-toluidide.

The constitution assigned to these additive compounds is based on reactions which are set out for the compound (VII) derived from 1-chloro-2-toluene-*p*-sulphonamidonaphthalene. Thermal decomposition gave in good yield 1 : 3 : 4-trichloro-2-toluene-*p*-sulphonamidonaphthalene. Reduction with zinc dust and acetic acid gave 1-chloro-2-toluene-*p*-sulphonamidonaphthalene, with intermediate formation of an intensely coloured solution. With pyridine there was produced a yellow compound, readily soluble in acids and regarded as (VIII), analogous to (IX), obtained by interaction of picramic acid with toluene-*p*-sulphonyl chloride in pyridine (Bell, *J.*, 1931, 2344). That the pyridine residue does not displace the halogen atoms present in position 1 is shown by the conversion of compound (VI; X = Br, R = $SO_2{\cdot}C_6H_4Me$) into the corresponding 1-bromo-4-chloropyridinium compound (as VIII). The aniline residue in compound (X) is placed in position 3 for the same reason. Base (XI) is obtained irrespective of the identity of the sulphonyl group originally present. The thermal decomposition of mixed halogen compounds such as (VI; X = Br) resulted in evolution of bromine, but the reaction was complex and the solid products were not identified.

These additive compounds are somewhat akin in structure to (XII; X = Cl), obtained by passing chlorine into a cold chloroform solution of 1-chloro-2-acetonaphthalide (Claus and Philipson, *loc. cit.*) and (XIII), obtained by interaction of chlorine and a benzene suspension of β-naphthylamine hydrochloride (Durand and Huguenin A.G., D.R.-P. 400,254). Both products were, therefore, re-examined.

It was found that (XII; X = Cl) passed smoothly into 1 : 3 : 4-trichloro-2-acetonaphthalide when heated. The reactions with pyridine and aniline were vigorous, but identifiable products were not isolated. In hot acetic acid the compound suffered profound decomposition, and no crystalline material could be isolated from the solution. In an unsuccessful attempt to repeat the preparation of compound (XII; X = Br), obtained by Claus and Jack (*loc. cit.*) by the action of chlorine on a chloroform solution of 1-bromo-2-acetonaphthalide, a considerable amount (*ca.* 15%) of 1 : 4-dichloro-2-acetonaphthalide was isolated.

Compound (XIII) is surprisingly stable. It was precipitated unchanged after addition of water to an acetic anhydride solution which had been set aside for one week, and was recovered unchanged from solution in cold aniline. Pyridine brought about rapid decomposition to give yellow amorphous products. The dichloro-base obtained by reduction (D.R.-P. 420,754) was shown by conversion into 1 : 3-dichloronaphthalene to be 1 : 3-dichloro-2-naphthylamine. It may be noted that a 2-naphthylamine with halogen atoms in positions 1 and 3 reacts sluggishly with toluene-*p*-sulphonyl chloride but then gives the ditoluene-*p*-sulphonamide rather than the monosulphonamide (compare the behaviour of certain nitroamines; Bell, *J.*, 1929, 2787). With chlorine in acetic acid 1 : 3-dichloro-2-acetonaphthalide gave a poor yield of 1 : 3 : 4-trichloro-2-acetonaphthalide and, similarly, 1 : 3-dichloro-2-toluene-*p*-sulphonamidonaphthalene yielded the 1 : 3 : 4-trichloro-compound.

The following tentative suggestions are offered in regard to the halogenation of β-naphthylamine and its derivatives :

(*a*) Entry into positions 1 and 6 represents normal attack by " molecular " halogen under the influence of the directing group in position 2.

(*b*) Entry into position 3 results from attack by positive halogen or, less probably, a halogen radical.

(*c*) Entry into position 4 involves elimination of halogen halide from a previously formed additive compound.

## Experimental

*Bromination of* 1-*Chloro*-2-*toluene*-p-*sulphonamidonaphthalene*.—(*a*) Bromine (1·5 g.) in acetic acid (3 c.c.) was added to the sulphonamidonaphthalene (3 g.) in warm acetic acid (20 c.c.). No crystallisation occurred even after overnight storage, so water was added. The resultant oil slowly solidified; repeated crystallisation from acetic acid gave 6-*bromo*-1-*chloro*-2-*toluene*-p-*sulphonamidonaphthalene* (1·2 g.) as needles, m. p. 163° (Found: C, 50·0; H, 3·2. $C_{17}H_{13}O_2NSClBr$ requires C, 49·7; H, 3·2%). This was hydrolysed by cold sulphuric acid (about 1 hr. required), and the resultant base acetylated to give 6-bromo-1-chloro-2-acetonaphthalide, m. p. 224°, alone or mixed with an authentic sample.

(*b*) Bromine (1·3 g.) in chloroform was added to the sulphonamidonaphthalene (2·6 g.) in chloroform, and the mixture set aside for 2 days. The deposit (1·3 g.) was slightly impure 6-bromo-1-chloro-2-naphthylamine hydrobromide. The filtrate on concentration gave 6-bromo-1-chloro-2-toluene-*p*-sulphonamidonaphthalene (1·0 g.).

(*c*) Bromine (1 mol.), diluted with light petroleum, was added to a cold solution of the compound in pyridine. After 3 hr. the mixture was decomposed with hydrochloric acid. The resultant oil soon solidified, and, after crystallisation from acetic acid, 3-*bromo*-1-*chloro*-2-*toluene*-p-*sulphonamidonaphthalene* formed needles, m. p. 186° (Found: C, 49·8; H, 3·3%). It was hydrolysed by cold sulphuric acid to 3-*bromo*-1-*chloro*-2-*naphthylamine*, needles, m. p. 100° (from methanol) (Found: C, 46·8; H, 2·7. $C_{10}H_7NClBr$ requires C, 46·5; H, 2·8%), and was converted by the usual nitrous acid–ethanol method to 3-bromo-1-chloronaphthalene, needles, m. p. 60°, from methanol–acetone (Hodgson and Hathway, *J.*, 1944, 538, give m. p. 60°). By interaction with acetic anhydride this base gave 3-*bromo*-1-*chloro*-2-*acetonaphthalide*, prisms, m. p. 204—206°, from acetic acid (Found: C, 48·2; H, 3·0. $C_{12}H_9ONClBr$ requires C, 48·2; H, 3·1%).

*Bromination of* 1-*Bromo*-2-*toluene*-p-*sulphonamidonaphthalene*.—(*a*) Addition of bromine (1 mol.) to the compound, m. p. 108°, in acetic acid gave a solution which was kept overnight and then diluted with water. The pasty product, after several recrystallisations from ethanol, furnished 1 : 6-dibromo-2-toluene-*p*-sulphonamidonaphthalene in poor yield.

(*b*) Bromine (1·1 g.) was added to the monobromo-compound (2·6 g.) in a small quantity of chloroform. After 2 days, 1 : 6-dibromo-2-naphthylamine hydrobromide (1·3 g.) was filtered off, and the filtrate diluted with light petroleum to give 1 : 6-dibromo-2-toluene-*p*-sulphonamidonaphthalene (1·2 g.).

2-*Bromo*-4 : 6-*dichlorotoluene*-p-*sulphonanilide*.—Bromination of 2 : 4-dichlorotoluene-*p*-sulphonanilide in pyridine solution readily gave the *bromodichloro*-compound, which formed needles, m. p. 160°, from acetic acid (Found: C, 39·8; H, 2·6. $C_{13}H_{10}O_2NSCl_2Br$ requires C, 39·5; H, 2·5%).

*Experiments with* N-*Bromosuccinimide*.—(*a*) 1-Chloro-2-acetonaphthalide was unchanged after being boiled in carbon tetrachloride with the reagent for 6 hr.

(*b*) Addition of the reagent to a boiling solution of 2-benzenesulphonamido-1-chloronaphthalene in carbon tetrachloride soon led to liberation of bromine. After 5 hr.' heating a brown sticky mass was obtained which was not examined further.

(*c*) Addition of the reagent (2 mol.) to 2-toluene-*p*-sulphonamidonaphthalene in pyridine, decomposition of the mixture with hydrochloric acid, and recrystallisation of the precipitate from acetic acid gave the 1 : 3-dibromo-derivative, m. p. 159°, in good yield.

(*d*) 2 : 4-Dichlorotoluene-*p*-sulphonanilide with the reagent (1 mol.) as in (*c*) gave an almost quantitative yield of the 6-bromo-derivative.

(*e*) 1-Nitro-2-toluene-*p*-sulphonamidonaphthalene with the reagent (1 mol.) as in (*c*) gave an almost quantitative yield of the 3-bromo-derivative, which crystallised from *o*-dichlorobenzene in rosettes, m. p. 237° (Consden and Kenyon, *J.*, 1935, 1593, give m. p. 237—239°).

(*f*) β-Naphthylamine, in pyridine, reacted briskly with the reagent (2 mol.). The product on decomposition with hydrochloric acid, gave a small amount of a yellow solid and an uncrystallisable black oil.

*Experiments with* N-*Chlorosuccinimide*.—(*a*) On addition of the reagent (1 mol.) to 1-chloro-2-toluene-*p*-sulphonamidonaphthalene in pyridine heat was evolved and the mixture became very dark. On decomposition with hydrochloric acid a plastic mass was precipitated and the solution

contained a pyridinium salt, which could be precipitated by addition of ammonium hydroxide. The plastic mass gave the original compound as the only isolable solid.

(*b*) 2 : 4-Dichlorotoluene-*p*-sulphonanilide treated as in (*a*) was recovered unchanged.

(*c*) 2-Toluene-*p*-sulphonamidonaphthalene treated as in (*a*) gave the 1-chloro-derivative, m. p. 130—131°.

(*d*) 2-Benzenesulphonamido-1-bromonaphthalene behaved as in (*a*) but the sticky mass, after repeated crystallisation from acetic acid, gave a *2-benzenesulphonamido-1-bromo-dichloronaphthalene* as prisms, m. p. 198° (Found: C, 45·3, 45·4; H, 2·6, 2·4. $C_{16}H_{10}O_2NSCl_2Br$ requires C, 44·5; H, 2·3%). *2-Benzenesulphonamido-1-bromonaphthalene* was obtained (*a*) from 1-bromo-2-naphthylamine or (*b*) by the addition of bromine (1 mol.) to 2-benzenesulphonamidonaphthalene in chloroform; the mixture was filtered from a small precipitate of hydrobromide, and the filtrate diluted with light petroleum. The bromo-compound crystallised from ethanol or acetic acid in needles, m. p. 135° (Found: N, 3·7. $C_{16}H_{12}O_2NSBr$ requires N, 3·9%).

*Chlorine Addition Compounds of Type* (VI).—These compounds were prepared by passing a slight excess of chlorine into a warm acetic acid or chloroform solution of the sulphonamidonaphthalene. The additive compound crystallised from the solution in acetic acid or on addition of light petroleum to the chloroform solution, and was purified by crystallisation from acetic acid, benzene, or chloroform. The following compounds were thus obtained: 1 : 1 : 3 : 4-*tetrachloro*-1 : 2 : 3 : 4-*tetrahydro*-2-*toluene*-p-*sulphonimidonaphthalene* (VII), needles, m. p. 164° (Found: C, 46·6; H, 3·1; Cl, 33·5. $C_{17}H_{13}O_2NSCl_4$ requires C, 46·7; H, 3·0; Cl, 32·5%); 1-*bromo*-1 : 3 : 4-*trichloro*-1 : 2 : 3 : 4-*tetrahydro*-2-*toluene*-p-*sulphonimidonaphthalene* (VI; X = Br, R = $SO_2{\cdot}C_6H_4Me$), mass of fine needles, m. p. 179° (decomp.) (Found: C, 42·8; H, 2·8. $C_{17}H_{13}O_2NSCl_3Br$ requires C, 42·3; H, 2·7%); *2-benzenesulphonimido*-1 : 1 : 3 : 4-*tetrachloro*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, prisms, m. p. 143° (Found: C, 45·8; H, 2·7. $C_{16}H_{11}O_2NCl_4S$ requires C, 45·4; H, 2·6%); and 1 : 1 : 3 : 4-*tetrachloro*-1 : 2 : 3 : 4-*tetrahydro*-2-m-*nitrobenzenesulphonimidonaphthalene*, prisms, m. p. 192° (Found: C, 41·0; H, 2·2. $C_{16}H_{10}O_4N_2Cl_4S$ requires C, 41·0; H, 2·1%). A small amount of 1 : 3 : 4-*trichloro*-2-m-*nitrobenzenesulphonamidonaphthalene* was formed as a by-product in this experiment; it crystallised from a large quantity of boiling acetic acid in prisms, m. p. 226° (Found: S, 7·3. $C_{16}H_9O_4N_2Cl_3S$ requires S, 7·4%). 1 : 3 : 4-Trichloro-2-naphthylamine was recovered unchanged from its pyridine solution with *m*-nitrobenzenesulphonyl chloride. 1-*Chloro*-2-m-*nitrobenzenesulphonamidonaphthalene*, prepared either from 1-chloro-2-naphthylamine or by chlorination of 2-*m*-nitrobenzenesulphonamidonaphthalene in hot acetic acid solution, crystallised from acetic acid in prisms, m. p. 135° (Found: C, 52·8; H, 3·1. $C_{16}H_{11}O_4N_2ClS$ requires C, 52·9; H, 3·0%).

*Reactions of the Addition Compounds.*—(a) *Heat.* A small amount of the addition compound was kept at about 10° above its m. p. until evolution of hydrogen chloride ceased (about ¼ hr.). The dark residue when crystallised from acetic acid gave an almost quantitative yield of the corresponding 1 : 3 : 4-trichloro-2-sulphonamidonaphthalene.

The addition compounds containing bromine in position 1 under these conditions evolved bromine. The residues yielded small amounts of crystalline solids which were not identified.

(b) *Zinc dust–acetic acid.* Addition of zinc dust to a warm solution of the addition compound in acetic acid resulted in vigorous reaction and the production of a deep damson or permanganate colour which was completely discharged on addition of excess of zinc dust. The hot solution was filtered and slightly diluted whereupon the 1-chloro-2-sulphonamidonaphthalene crystallised.

1-Bromo-1 : 3 : 4-trichloro-1 : 2 : 3 : 4-tetrahydro-2-toluene-*p*-sulphonimidonaphthalene gave material, m. p. 108—109° (after one crystallisation from benzene–light petroleum), corresponding to almost pure 1-chloro-2-toluene-*p*-sulphonamidonaphthalene (large depression in m. p. on admixture with 1-bromo-2-toluene-*p*-sulphonamidonaphthalene).

(c) *Pyridine.* On addition of 1-bromo-1 : 3 : 4-trichloro-1 : 2 : 3 : 4-tetrahydro-2-toluene-*p*-sulphonimidonaphthalene to cold pyridine there was considerable heat evolution. Excess of hydrochloric acid was added, the mixture filtered, and the filtrate neutralised with ammonia solution. *Anhydro*-N-(4-*bromo*-1-*chloro*-3-*toluene*-p-*sulphonamido*-2-*naphthyl*)*pyridinium hydroxide* separated as pale yellow crystals, m. p. 266° (decomp.) after reprecipitation from dilute acetic acid by ammonia solution (Found: C, 54·6, 54·3; H, 3·9, 3·8; S, 6·6. $C_{22}H_{18}O_2N_2SClBr$ requires C, 54·0; H, 3·7; S, 6·5%).

Addition of hydrochloric acid to the deep yellow pyridine solution of 1 : 1 : 3 : 4-tetrachloro-1 : 2 : 3 : 4-tetrahydro-2-toluene-*p*-sulphonimidonaphthalene gave a small precipitate, m. p. *ca.* 190°, and a filtrate from which ammonia solution precipitated yellow crystals of *anhydro*-N-(1 : 4-*dichloro*-3-*toluene*-p-*sulphonamido*-2-*naphthyl*)*pyridinium hydroxide* (VIII), m. p. 274°

(decomp.) after reprecipitation from solution in dilute acetic acid (Found: C, 58·7; H, 3·9; Cl, 15·2; S, 7·2. $C_{22}H_{18}O_2N_2SCl_2$ requires C, 59·3; H, 4·0; Cl, 15·9; S, 7·2%). The material, m. p. *ca.* 190°, after repeated crystallisation from acetic acid gave 1 : 3 : 4-*trichloro*-2-*toluene*-p-*sulphonamidonaphthalene* as prisms, m. p. 212° (Found: Cl, 26·0. $C_{17}H_{12}O_2NSCl_3$ requires Cl, 26·6%).

(d) *Aniline.* 1 : 1 : 3 : 4-Tetrachloro-1 : 2 : 3 : 4-tetrahydro-2-toluene-*p*-sulphonimidonaphthalene reacted vigorously with cold aniline to give a clear solution which soon became semi-solid. Decomposition with dilute hydrochloric acid gave 3-*anilino*-1 : 4-*dichloro*-2-*toluene*-p-*sulphonamidonaphthalene* (X) (Found: C, 60·3; H, 4·0. $C_{23}H_{18}O_2N_2Cl_2S$ requires C, 60·4; H, 3·9%), which formed needles, m. p. 201° after repeated recrystallisation from acetic acid or benzene–light petroleum to free it from deep-violet impurities, and was hydrolysed by cold sulphuric acid to 2-*amino*-3-*anilino*-1 : 4-*dichloronaphthalene* (XI) (Found: C, 63·2; H, 4·0. $C_{16}H_{12}N_2Cl_2$ requires C, 63·4; H, 4·0%). The latter crystallised from ethanol or benzene in needles, m. p. 167°, and was recovered unchanged after being boiled with acetic anhydride; it sublimed unchanged from a strongly heated mixture with litharge.

In the same way 1-bromo-1 : 3 : 4-trichloro-1 : 2 : 3 : 4-tetrahydro-2-toluene-*p*-sulphonimidonaphthalene gave 3-*anilino*-1-*bromo*-4-*chloro*-2-*toluene*-p-*sulphonamidonaphthalene*, needles, m. p. 210°, from acetic acid (Found: N, 5·3; S, 5·9. $C_{23}H_{18}O_2N_2ClBrS$ requires N, 5·6; S, 6·4%), and 2-*amino*-3-*anilino*-1-*bromo*-4-*chloronaphthalene*, needles, m. p. 164° (decomp.), from benzene (Found: N, 8·2. $C_{16}H_{12}N_2ClBr$ requires N, 8·0%).

1 : 1 : 3 : 4-Tetrachloro-1 : 2 : 3 : 4-tetrahydro-2-*m*-nitrobenzenesulphonimidonaphthalene gave 3-*anilino*-1 : 4-*dichloro*-2-m-*nitrobenzenesulphonamidonaphthalene*, rosettes, m. p. 168° (from acetic acid) (Found: C, 53·5; H, 3·2. $C_{22}H_{15}O_4N_3Cl_2S$ requires C, 54·1; H, 3·1%). This compound was recovered after 8 hr. in cold concentrated sulphuric acid or after being boiled with ethanolic hydrogen chloride.

2-Benzenesulphonimido-1 : 1 : 3 : 4-tetrachloro-1 : 2 : 3 : 4-tetrahydronaphthalene gave 3-*anilino*-2-*benzenesulphonamido*-1 : 4-*dichloronaphthalene*, needles, m. p. 204° (from acetic acid) (Found: C, 60·2; H, 3·8. $C_{22}H_{16}O_2N_2Cl_2S$ requires C, 59·6; H, 3·6%). Hydrolysis of this by cold sulphuric acid gave material, m. p. 158—160°, which was separated by crystallisation from benzene into a small amount of a sparingly soluble compound, m. p. 230° (unidentified), and rosettes of 2-amino-3-anilino-1 : 4-dichloronaphthalene.

*Experiments with* 1-*Halogenated*-2-*acetonaphthalides.*—(*a*) 1 : 1 : 2 : 3 : 4-Pentachloro-1 : 2 : 3 : 4-tetrahydro-2-acetonaphthalide (XII; X = Cl) was heated at 160° for a few minutes and the product then crystallised from acetic acid giving 1 : 3 : 4-trichloro-2-acetonaphthalide.

(*b*) By passage of chlorine into a cold chloroform solution of 1-bromo-2-acetonaphthalide (6 g.) there were obtained a precipitate (1·2 g.) of the hydrochloride, m. p. 140° (decomp.), and a filtrate from which light petroleum precipitated first gummy material and then a solid (*ca.* 1 g.), m. p. 160—170°. This after repeated recrystallisation from ethanol gave pure 1 : 4-dichloro-2-acetonaphthalide, m. p. 217° alone or mixed with an authentic sample.

(*c*) 1-Bromo-2-acetonaphthalide hydrochloride was maintained at 150° until the vigorous decomposition was complete. The dark product was essentially 1-bromo-2-acetonaphthalide (Found: loss, 11·2. $C_{12}H_{10}ONBr,HCl$ requires loss, 12·1%). It may be noted that if the hydrochloride were structurally 1-bromo-1-chloro-1 : 2-dihydro-2-acetonaphthalide decomposition to give 1-chloro-2-acetonaphthalide, with a loss in weight of 27%, would be possible.

1 : 1 : 3 : 3 : 5-*Pentachloro*-2-*chloroimino*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII) was prepared by the method of Durand and Huguenin A.G. (*loc. cit.*) but a clear solution was not obtained at the end of the chlorination process. The insoluble material, of high decomposition point, was filtered off and decomposed with ammonia solution. It gave a sticky product which was boiled with ethanol and filtered whilst hot. The insoluble residue formed yellow needles, m. p. 285° (from *o*-dichlorobenzene), and appeared to be 1 : 2·5 : 6-dibenzophenazine. The alcoholic filtrate gave crude 1-chloro-2-naphthylamine, best purified as the acetyl derivative, m. p. 146°.

The pentachloro-compound was precipitated unchanged by addition of water to a solution in acetic anhydride, which had been kept for 1 week. It was also recovered from solution in cold aniline but was rapidly decomposed by pyridine to give yellow amorphous products.

Reduction (D.R.-P. 420,754) of the pentachloro-compound (24 g.) gave dichloro-2-naphthylamine (10 g.) and a mixture (10 g.) of chloronaphthols, apparently mainly 1 : 3-dichloro-2-naphthol (acetyl derivative, needles, m. p. 74—76°). The base was shown to be 1 : 3-dichloro-2-naphthylamine by smooth deamination to 1 : 3-dichloronaphthalene, needles, m. p. 61° (from ethanol) (Cleve, *Ber.*, 1887, **20**, 449, gives m. p. 61°; 1 : 2-dichloronaphthalene has m. p. 35°).

1 : 3-Dichloro-2-naphthylamine could be crystallised unchanged from acetic anhydride but

with acetic anhydride containing a drop of sulphuric acid gave 1 : 3-*dichloro*-2-*acetonaphthalide*, prisms, m. p. 198—200° (from acetic acid) (Found : C, 56·6; H, 3·5. $C_{12}H_9ONCl_2$ requires C, 56·7; H, 3·5%). With toluene-*p*-sulphonyl chloride (1 mol.) in pyridine the base gave a difficultly separable mixture; with 2 mol. it gave 1 : 3-*dichloro*-2-*di*(*toluene*-p-*sulphonyl*)*amino*-*naphthalene*, prisms, m. p. 216° (from acetic acid) (Found : S, 12·3. $C_{24}H_{19}O_4NCl_2S_2$ requires S, 12·2%). This was smoothly hydrolysed by warm piperidine to give 1 : 3-*dichloro*-2-*toluene*-p-*sulphonamidonaphthalene*, needles, m. p. 185°, from acetic acid (Found : S, 8·75. $C_{17}H_{13}O_2NSCl_2$ requires S, 8·75%).

1 : 3 : 4-*Trichloro*-2-*di*(*toluene*-p-*sulphonyl*)*aminonaphthalene*, obtained by interaction of 1 : 3 : 4-trichloro-2-naphthylamine with toluene-*p*-sulphonyl chloride (2 mols.) in pyridine, crystallised from acetic acid in prisms, m. p. 248° (Found : S, 11·7. $C_{24}H_{18}O_4NCl_3S_2$ requires S, 11·5%). It was converted into the monotoluenesulphonamide by dissolution in warm piperidine.

*Miscellaneous Chlorinations.*—(*a*) By passage of chlorine into a solution of 1 : 3-dichloro-2-toluene-*p*-sulphonamidonaphthalene there was obtained 1 : 3 : 4-trichloro-2-toluene-*p*-sulphonamidonaphthalene, unchanged after further treatment in acetic acid solution with chlorine.

(*b*) Chlorine was passed into a hot solution of 1 : 3-dichloro-2-acetonaphthalide in chloroform, the solvent chloroform was evaporated, and the residue was boiled with benzene; about half of the starting material was recovered and the product was an uncrystallisable gum. This experiment was repeated with acetic acid as solvent; a small yield of 1 : 3 : 4-trichloro-2-acetonaphthalide was obtained but most of the compound had been converted into a pale yellow, uncrystallisable gum.

(*c*) Passage of chlorine into a cold chloroform solution of 1-iodo-2-toluene-*p*-sulphonamidonaphthalene (Consden and Kenyon, *J.*, 1935, 1591) led to rapid liberation of iodine, and no crystalline product could be obtained.

(*d*) No identified product could be isolated from the reaction of 1-nitro-2-toluene-*p*-sulphonamidonaphthalene with chlorine in either chloroform or acetic acid.

(*e*) Chlorination of 1-toluene-*p*-sulphonamidonaphthalene in either acetic acid or chloroform led to the 4-chloro- and then the 2 : 4-dichloro-derivative (m. p. 192°), but there was then no further reaction.

(*f*) 2 : 4-Dichlorotoluene-*p*-sulphonanilde was recovered after treatment with chlorine in acetic acid solution.

(*g*) 1-*Chloro*-2-*toluene*-p-*sulphonmethylamidonaphthalene*, prepared (i) by the methylation of 1-chloro-2-toluene-*p*-sulphonamidonaphthalene and (ii) by the chlorination of 2-toluene-*p*-sulphonmethylamidonaphthalene in acetic acid solution, crystallised from acetic acid or benzene–light petroleum in needles, m. p. 123—124° (Found : C, 62·6; H, 4·7. $C_{18}H_{16}O_2NClS$ requires C, 62·5; H, 4·6%). On chlorination in chloroform solution this compound gave an uncrystallisable resin.

(*h*) 1 : 4-*Dichloro*-2-*toluene*-p-*sulphonamidonaphthalene*, prepared by interaction of 1 : 4-dichloro-2-naphthylamine (Clemo and Legg, *J.*, 1947, 543) and toluene-*p*-sulphonyl chloride in pyridine, crystallised from acetic acid in needles, m. p. 144° (Found : C, 55·7; H, 3·6. $C_{17}H_{13}O_2NSCl_2$ requires C, 55·7; H, 3·6%). Passage of chlorine into a solution of this compound gave a very small amount of a compound, which formed prisms, m. p. 230°, from acetic acid, and appeared to be an isomer of the starting material (Found : C, 55·5; H, 3·7%).

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## 604. *The So-called* "1-*Fluoro*-3 : 4-*dinitrobenzene.*"

By H. Suschitzky.

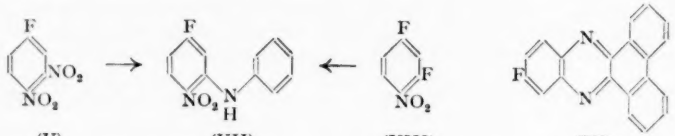
The so-called "1-fluoro-3 : 4-dinitrobenzene" (4-fluoro-1 : 2-dinitrobenzene) which Cannoni de Degiorgi and Zappi (*Anal. Asoc. Quím. Argentina*, 1940, **28**, 72) obtained by a Balz–Schiemann reaction on 3 : 4-dinitroaniline hydrochloride has been shown to be identical with 1-chloro-4-fluoro-2-nitrobenzene, the 4-nitro-group being replaced by chlorine during the diazotisation. The true 4-fluoro-1 : 2-dinitrobenzene has been prepared by nitration of *m*-fluoronitrobenzene, and its structure confirmed.

Cannoni de Degiorgi and Zappi (*Anal. Asoc. Quím. Argentina*, 1940, **28**, 72) have assigned to a yellow substance of m. p. 34° which they obtained by a Schiemann reaction on 3 : 4-dinitroaniline hydrochloride (I) the structure of 4-fluoro-1 : 2-dinitrobenzene (V) and to the intermediate borofluoride that of (II).

Analytical figures for substance (II) were not quoted, nor was an analysis for nitrogen given for (V). Since 4-fluoro-1 : 2-dinitrobenzene was needed for a wider investigation, this preparation was repeated; it gave a substance of similar physical properties (m. p. 35°) but of the formula $C_6H_3O_2NClF$, one of the nitro-groups having been replaced by chlorine. The exchange had not taken place during formation of the hydrochloride, because 3 : 4-dinitroaniline could be recovered from its salt. Since, however, the diazonium borofluoride contained chlorine, it was concluded that the replacement reaction had occurred during the diazotisation. Cannoni de Degiorgi and Zappi's compound was identified as 1-chloro-4-fluoro-2-nitrobenzene (IV), m. p. 35·9° (Ingold and Vass, *J.*, 1928, 2262), by a mixed-melting-point determination with an authentic specimen. The Schiemann reaction on 3 : 4-dinitroaniline (I) in hydrochloric acid leads, therefore, to the borofluoride (III) which, on pyrolysis, gives the chloro-compound (IV).

$$\underset{\text{(I)}}{3:4:1\text{-}(NO_2)_2\cdot C_6H_3\cdot NH_3Cl} \longrightarrow \underset{\text{(II)}}{3:4:1\text{-}(NO_2)_2C_6H_3\cdot N_2BF_4} \longrightarrow \underset{\text{(III)}}{3:4:1\text{-}NO_2\cdot C_6H_3Cl\cdot N_2BF_4} \longrightarrow \underset{\text{(IV)}}{3:4:1\text{-}NO_2\cdot C_6H_3ClF}$$

Expulsion of a nitro-group by chlorine during diazotisation has been recorded by, *e.g.*, Meldola and Eyre (*J.*, 1901, 1077) for polynitroanisidines, and Schiemann and Ley (*Ber.*, 1936, **69**, 960) for 1-nitro-2-naphthylamine. In each case elimination of the nitro-group follows the formation of the positively charged diazonium group which, by virtue of its high electron-attracting effect ($-I$, $-T$) presumably renders the *ortho*- or *para*-position particularly vulnerable to the attack of a nucleophilic chlorine ion. It is of interest that diazotisation of 3 : 4-dinitroaniline in sulphuric acid does not lead to the replacement of a nitro-group.



(V) (VII) (VIII) (VI)

The true 4-fluoro-1 : 2-dinitrobenzene (V) was readily obtained by nitration of *m*-fluoronitrobenzene. The nitration product possesses two adjacent nitro-groups, because reduction, followed by addition of phenanthraquinone, yielded phenanthrazine or 11-fluorophenanthrazine (VI; for numbering see Ring Index No. 3252), according to the conditions of the reaction. The position of the fluorine atom relative to that of the two nitro-groups is established by the fact that the same fluoronitrodiphenylamine (VII) resulted from the condensation of aniline with the fluorodinitrobenzene (V) or with 2 : 4-difluoro-1-nitrobenzene (VIII).

The use of the strongly nucleophilic piperidine for determination of structure (Le Fèvre and Turner, *J.*, 1927, 1113) also proved of diagnostic value, because treatment of compound (V) or (VIII) yielded the same 1-nitro-2 : 4-dipiperidinobenzene.

## Experimental

Decompositions of diazonium borofluorides were carried out in a current of dry nitrogen. Boron trifluoride fumes were thereby readily removed. The inert atmosphere reduced the formation of phenolic by-products and rendered the decomposition of large quantities controllable.

*The Alleged "* **1-*Fluoro*-3 : 4-*dinitrobenzene*** *"* (**1-*Chloro*-4-*fluoro*-2-*nitrobenzene***).—The method of Cannoni de Degiorgi and Zappi (*Anal. Asoc. Quím. Argentina*, **1940**, **28**, 71) was followed, except for the hydrolysis of **3** : 4-dinitroacetanilide, which was carried out with ethanol (5 vols.)–concentrated sulphuric acid (1 vol.), which gave a cleaner product and a higher yield. The so-called " 3 : 4-dinitrobenzenediazonium borofluoride " (4-chloro-3-nitrobenzenediazonium borofluoride), m. p. 158—159° (decomp.), gave a positive test for chlorine. Cannoni de Degiorgi and Zappi (*loc. cit.*) give " decomp. 161°." On pyrolysis it yielded a pale-yellow substance which crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 35° alone or mixed with 1-chloro-4-fluoro-2-nitrobenzene (see below) (Found : C, 41·0; H, 1·6; N, 7·9; Cl, 20·7. Calc. for $C_6H_3O_2NClF$ : C, 41·0; H, 1·7; N, 8·0; Cl, 20·2%).

**1-*Chloro*-4-*fluoro*-2-*nitrobenzene*** (cf. Swarts, *Rec. Trav. chim.*, 1915, **35**, 131; Ingold and Vass, *J.*, 1928, 2262).—*p*-Chloroaniline (25 g.) was diazotised in aqueous (18%) hydrochloric acid (120 c.c.) with sodium nitrite solution (50%), and addition of sodium borofluoride solution (110 c.c. of 40%) precipitated colourless p-*chlorobenzenediazonium borofluoride*, m. p. 126° (decomp.) (35 g., 79%). Pyrolysis yielded *p*-chlorofluorobenzene, b. p. 130°/758 mm. (16 g., 80%). Swarts (*loc. cit.*) records b. p. 129·1—130·2°/757 mm. *p*-Chlorofluorobenzene (12·6 g.) afforded on nitration by Swarts's method (*loc. cit.*) a pale-yellow liquid mixture (13 g.) of 4-chloro-1- and 1-chloro-4-fluoro-2-nitrobenzene. This (5 g.) was warmed in alcoholic 0·1N-potassium hydroxide (82·5 c.c.) at 40° for ¾ hr.; conversion of the unwanted 4-chloro-1-fluoro-2-nitrobenzene into the corresponding chloronitrophenol was followed by titration of test samples (0·5 c.c.) with 0·1M-hydrochloric acid. When the titre no longer changed (40 min.), the mixture was neutralised with 0·01N-hydrochloric acid and extracted with ether. Evaporation of the dried ethereal extract afforded a pale-yellow solid, of m. p. 30° which could not be raised by recrystallisation. The substance (0·2 g.) was chromatographed in light petroleum (b. p. 60—80°; 100 c.c.) on alumina (activated alumina, P. Spence, Type H, 100—200 mesh; 1 × 10 cm.) with the solvent (420 c.c.) as eluant (50-c.c. fractions). From the final fractions nearly colourless 1-chloro-4-fluoro-2-nitrobenzene, m. p. 36°, was obtained on evaporation. Ingold and Vass (*loc. cit.*) give m. p. 35·9° (Found : C, 41·0; H, 1·8; N, 7·8; Cl, 20·4%).

**4-*Fluoro*-1 : 2-*dinitrobenzene*.**—(*a*) *m*-Fluoronitrobenzene (12·0 g.) (Schiemann and Pillarsky, *Ber.*, 1929, **62**, 3035) was added dropwise with stirring to a 1 : 1-mixture (130 c.c.) of nitric acid (*d* 1·5) and sulphuric acid (*d* 1·84). The mixture was kept at 50° for 0·5 hr. and then poured on ice (300 g.). The lemon-coloured solid was collected, washed with sodium carbonate solution (10%) until the wash-liquid was colourless, and then with water. Recrystallisation from ethanol and then light petroleum (b. p. 60—80°) afforded nearly colourless, prismatic needles (up to 3·5 cm.) of 4-*fluoro*-1 : 2-*dinitrobenzene*, m. p. 55—56° (13·2 g. crude; 11·4 g. pure, 74%) [Found : C, 38·8; H, 1·7; N, 15·1. $C_6H_3O_4N_2F$ requires C, 38·7; H, 1·6; N, 15·0%. Estimation of nitro-groups : 0·31 G. consumed 0·180 g. of $SnCl_2$. $C_6H_3F(NO_2)_2$ requires 0·185 g.

(*b*) Finely powdered **3** : 4-dinitroaniline (4·5 g.) (Wender, *Gazzetta*, 1889, **19**, 225) was triturated with 50% sulphuric acid (25 c.c.) and then diazotised with solid sodium nitrite at about −10°. Addition of sodium borofluoride solution (5·4 g., 40%) yielded pale-brown 3 : 4-dinitrobenzenediazonium borofluoride (2 g., 29%), decomp. 166—169°. Thermal decomposition afforded a pale-yellow solid (0·14 g., 10%), m. p. 54° alone or mixed with a specimen prepared as described under (*a*).

*Phenanthrazine*.—4-Fluoro-1 : 2-dinitrobenzene (0·5 g.) was reduced by Jones and Robinson's method (*J.*, 1917, 912) and then treated with a hot solution of phenanthraquinone (0·8 g.) in 50% aqueous sodium hydrogen sulphite solution (6 c.c.) buffered with sodium acetate (1 g.). A solid, m. p. 216°, separated which showed an undepressed m. p. when mixed with an authentic sample of phenanthrazine.

**11-*Fluorophenanthrazine*.**—4-Fluoro-1 : 2-dinitrobenzene (0·4 g.) was shaken in ethanol (20 c.c.) under hydrogen at room temperature and pressure in presence of Adams's platinum catalyst (50 mg.). After filtration the ethanol was evaporated off under diminished pressure, the residual solid was taken up in ether, and the hydrochloride of the base precipitated with dry hydrogen chloride. **4-*Fluoro*-o-*phenylenediamine*** (0·19 g., 70·5%) was obtained by treatment of the salt with concentrated ammonia solution. It crystallised from benzene as greyish

needles, m. p. 88—89° (Found: C, 57·4; H, 5·3; N, 22·4. $C_6H_7N_2F$ requires C, 57·1; H, 5·6; N, 22·2%). A mixture of the diamine (0·1 g.) in ethanol (1 c.c.) and phenanthraquinone (0·17 g.) in acetic acid (2 c.c.), warmed for a few minutes, gave 11-*fluorophenanthrazine* as pale yellow flakes, m. p. 226° (Found: C, 80·7; H, 3·5; N, 9·3. $C_{20}H_{11}N_2F$ requires C, 80·5; H, 3·7; N, 9·4%).

5-*Fluoro*-2-*nitrodiphenylamine*.—(*a*) 4-Fluoro-1 : 2-dinitrobenzene (6 g.) and freshly distilled aniline (14·5 c.c.) were heated together on a steam-bath for 7 hr. with gradual addition of finely powdered sodium acetate (2·4 g.). The dark-red mixture was set aside at room temperature for 1 day and then poured into 20% hydrochloric acid (100 c.c.) to remove excess of aniline. The brown solid which separated was washed free from acid and recrystallised from ethanol. 5-*Fluoro*-2-*nitrodiphenylamine* (4·8 g., 64·5%) separated as golden-yellow needles, m. p. 93—94° (Found: C, 62·2; H, 3·9; N, 12·1. $C_{12}H_9O_2N_2F$ requires C, 62·0; H, 3·9; N, 12·0%).

(*b*) A mixture of 2 : 4-difluoro-1-nitrobenzene (8·2 g.) (Schiemann, *J. pr. Chem.*, 1934, **140**, 97) and freshly distilled aniline (40 g.) was kept overnight at room temperature. (Alternatively the condensation could be effected by heating on a steam-bath for 0·5 hr.) An orange-red crystalline deposit appeared after 1 hr. The dark-red suspension was poured into a separator containing 20% aqueous hydrochloric acid (150 c.c.) and benzene (100 c.c.). The violet acid layer was run off and the brown benzene extract was repeatedly washed with 20% hydrochloric acid and finally dried. Evaporation of the solvent yielded a brown solid which was purified by steam-distillation and afforded 5-fluoro-2-nitrodiphenylamine (10 g., 84%) as lemon-coloured needles, m. p. 94° alone or mixed with a specimen prepared as described under (*a*).

1-*Nitro*-2 : 4-*dipiperidinobenzene*.—(*a*) To 4-fluoro-1 : 2-dinitrobenzene (0·5 g.), piperidine (2 c.c.) was added dropwise with cooling and, when the violent reaction had ceased, the mixture was boiled for 1 min. On addition of water (20 c.c.) an orange-coloured oil separated which, after being washed with water and dried in a desiccator, crystallised in contact with benzene. 1-Nitro-2 : 4-dipiperidinobenzene (0·5 g., 62%) separated from ethanol as orange-red needles, m. p. and mixed m. p. 63—64° (Found: N, 14·3. Calc. for $C_{16}H_{23}O_2N_3$: N, 14·5%). Le Fèvre and Turner (*J.*, 1927, 1113) give m. p. 63—64°.

(*b*) 2 : 4-Difluoro-1-nitrobenzene (0·5 g.) was treated with piperidine (2 c.c.) as described above, giving 1-nitro-2 : 4-dipiperidinobenzene (nearly quantitative yield), m. p. and mixed m. p. 63—64°

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## 605. *The Kinetics of the Reaction between Thallium*(III) *and Iron*(II) *in Aqueous Perchloric Acid.*

By K. G. ASHURST and W. C. E. HIGGINSON.

Contrary to previous work it is shown that iron(III) retards the rate of oxidation of iron(II) by thallium(III) in aqueous perchloric acid. This is consistent with the mechanism:

$$Tl(III) + Fe(II) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Tl(II) + Fe(III)$$

$$Tl(II) + Fe(II) \xrightarrow{k_2} Tl(I) + Fe(III)$$

The significance of the dependence of $k_1$ and $k_2/k_{-1}$ (reaction velocity constants) upon the hydrogen-ion concentration is discussed.

JOHNSON (*J. Amer. Chem. Soc.*, 1952, **74**, 959), investigating the kinetics of the reaction $Tl(III) + 2Fe(II) \longrightarrow Tl(I) + 2Fe(III)$, in dilute perchloric acid solution, showed that initially the reaction is of first order with regard to both thallium(III) and iron(II); a falling off apparent in the second-order rate plots after 60% reaction was attributed to small errors in the analytical method. The dependence of the rate upon the hydrogen-ion concentration was interpreted in terms of reaction between $TlOH^{++}$ and $Fe^{++}$, and between $TlO^{+}$ and $Fe^{++}$. Forchheimer and Epple (*ibid.*, p. 5772) used somewhat different conditions, in particular higher thallium(III) and iron(II) concentrations, in most of their experiments, and their method of analysis was different; they too noticed a decrease in

the rate of reaction after 60% reaction, but, unlike Johnson, they ascribed this effect to the presence of atmospheric oxygen, for in experiments in the absence of oxygen the effect was not observed. It is to be noted that all Johnson's experiments were done under nitrogen. In both these papers the authors concluded that the products, thallium(I) and iron(III), have no influence upon the rate of reaction, but they were unable to decide between the two most probable reaction schemes: in (i) the initial oxidation–reduction step is the 1-electron transfer reaction Tl(III) + Fe(II) $\longrightarrow$ Tl(II) + Fe(III), followed by Tl(II) + Fe(II) $\longrightarrow$ Tl(I) + Fe(III); in (ii) the 2-electron transfer reaction Tl(III) + Fe(II) $\longrightarrow$ Tl(I) + Fe(IV) is the first step, followed by Fe(IV) + Fe(II) $\longrightarrow$ 2Fe(III).

We now find that air has no significant effect upon the rate of reaction; we also conclude that in most of our experiments errors in the analysis of reaction samples are unimportant up to 90—95% reaction, and that the analytical accuracy is unaffected by alteration of the concentration of iron(III) present. Our kinetic results are summarised in the annexed Tables; the experiments in Tables 2 and 3 were performed after publication of Johnson's results, and to make comparison possible we used the same ionic strength as in his experiments.

TABLE 1.

| | Initial concentrations, M × $10^3$ | | | | Best values, linear for *ca.* 93%: | | With $k_2/k_{-1}$ = 27·0: | | Simple plot: $k_1$ (initial gradient) | % linear |
|---|---|---|---|---|---|---|---|---|---|---|
| Expt. | Fe(II) | Fe(III) | Tl(I) | Tl(III) | $k_1$ | $k_2/k_{-1}$ | $k_1$ | % linear | | |
| *A* | 2·33 | 0·065 | 0·85 | 32·6 | 0·95 | 27·0 | 0·95 | 98 | 0·95 | 65 |
| *B* | 2·34 | 4·84 | 0·85 | 32·6 | 0·95 | 27·0 | 0·95 | 97 | 0·90 | 50 |
| *C* | 2·32 | 12·05 | 0·85 | 32·6 | 0·92 | 30·7 | 0·97 | 94 | 0·79 | 45 |
| *D* | 2·32 | 19·24 | 0·85 | 32·6 | 0·81 | 41·7 | 0·98 | 92 | 0·69 | 40 |
| *E* | 2·29 | 0·098 | 11·82 | 32·6 | 0·96 | 19·9 | 0·96 | 95 | 0·96 | 60 |
| *F* | 2·29 | 0·102 | 23·66 | 32·6 | 0·96 | 18·3 | 0·94 | 96 | 0·94 | 60 |
| *G* | 2·15 | 12·20 | 22·25 | 32·6 | 0·99 | 21·8 | 0·92 | 86 | 0·78 | 35 |
| *H* | 7·34 | 0·643 | 71·1 | 8·15 | 0·96 | 21·2 | 0·95 | 87 | 0·94 | 65 |
| *I* | 7·34 | 0·643 | 0·242 | 8·15 | 0·99 | 23·6 | 0·97 | 94 | 0·99 | 65 |
| *J* | 7·30 | 48·57 | 47·5 | 8·15 | 0·89 | 22·7 | 0·83 | 85 | 0·67 | 35 |
| *K* | 7·30 | 48·57 | 0·242 | 8·15 | 0·80 | 32·8 | 0·86 | 85 | 0·67 | 35 |

$[H^+]$ = 1·00M; ionic strength = 1·60.

TABLE 2.

| | Initial concns., M × $10^3$ | | Best values, linear for *ca.* 93% | | With $k_2/k_{-1}$ = 19·4: | | Simple second-order plot: | |
|---|---|---|---|---|---|---|---|---|
| Expt. | Fe(II) | Fe(III) | $k_1$ | $k_2/k_{-1}$ | $k_1$ | % linear | $k_1$ | % linear |
| *L* | 5·96 | 0·018 | 1·80 | 19·4 | 1·80 | 98 | 1·80 | 60 |
| *M* | 5·96 | 0·192 | 1·78 | 19·4 | 1·78 | 97 | 1·74 | 50 |
| *N* | 5·74 | 0·237 | 1·83 | 19·4 | 1·83 | 96 | 1·79 | 70 |
| *O* | 5·54 | 10·10 | 1·74 | 27·6 | 1·84 | 83 | 1·67 | 45 |
| *P* | 5·59 | 28·05 | 1·65 | 25·6 | 1·84 | 88 | 1·34 | 35 |
| *Q* | 5·59 | 48·80 | 1·51 | 28·9 | 1·70 | 84 | 1·14 | 25 |

$[H^+]$ = 0·668M; ionic strength = 3·00; $[Tl(I)]$ = 1·65 × $10^{-4}$M; $[Tl(III)]$ = 6·12 × $10^{-3}$M.

The results in Tables 1 and 2 show that the reaction velocity constant, obtained from the initial gradient of the simple first- or second-order plot, decreases as the initial concentration of iron(III) is increased, and the curvature of these plots becomes more pronounced. This can be seen in Fig. 1, which shows the simple second-order plots, $\log [Fe(II)]_t/2[Tl(III)]_t$ against $t$, for experiments in Table 2. The experimental conditions were similar, except that the initial concentrations of iron(III) were increased from *L* to *Q*. Increases in the initial concentration of thallium(I) have no effect on the initial gradient, but cause a small alteration in the curvature of the simple plots towards the end of the reaction. As discussed on p. 3049, this effect is due to a side-reaction affecting the accuracy of the analytical procedure, and we conclude that, over the concentration range studied, thallium(I) has no significant effect upon the rate of reaction.

Accordingly, we suggest that the overall reaction must involve the following steps:

$$Tl(III) + Fe(II) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Tl(II) + Fe(III) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Tl(II) + Fe(II) \xrightarrow{k_2} Tl(I) + Fe(III) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The retarding effect of iron(III) is ascribed to the reversal of reaction (1). From this reaction scheme the expression

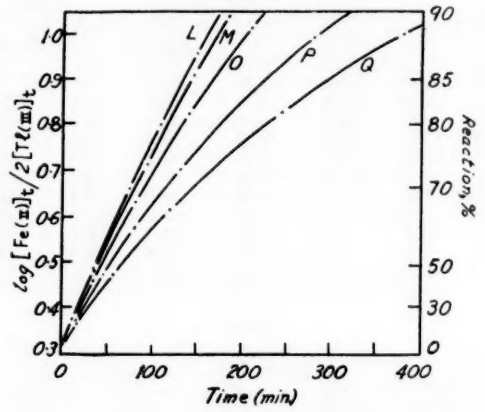
$$d[Fe(II)]/dt = -2k_1k_2[Fe(II)]^2[Tl(III)]/\{k_2[Fe(II)] + k_{-1}[Fe(III)]\} \quad . \quad . \quad (i)$$

can be deduced by making the stationary-state assumption $d[Tl(II)]/dt = 0$. If $a = [Fe(II)]_{initial}$, $b = 2[Tl(III)]_{initial}$, and $c = [Fe(III)]_{initial}$, integration gives:

$$\frac{k_{-1}(a+c)}{k_2 - k_{-1}\left(1 + \frac{a+c}{b-a}\right)} \cdot \frac{1}{[Fe(II)]_t} - \log_e \frac{[Fe(II)]_t}{2[Tl(III)]_t} = \frac{k_2(b-a)}{k_2 - k_{-1}\left(1 + \frac{a+c}{b-a}\right)} k_1 t + M \quad (ii)$$

a second-order kinetic equation modified by the term $1/[Fe(II)]_t$, $M$ being a constant. In first-order conditions, with thallium(III) in considerable excess over iron(II), $(b - a)$ and $2Tl(III)$ are both replaced by $b$. For first- or second-order conditions, if the appropriate value of $k_2/k_{-1}$ is known, the plot of the left-hand side of (ii) against $t$ will be linear for the whole reaction, and $k_1$ can be found. For each experiment, a value of $k_2/k_{-1}$ was selected

FIG. 1.




to give the best linear plot; in practice, linearity could be achieved up to about 95% of reaction. It can be seen from Tables 1 and 2 that there is much better constancy in the $k_1$ values obtained in this way than in those obtained from the initial gradients of simple first- or second-order plots. If the reaction scheme proposed is correct, the $k_2/k_{-1}$ value should be constant at a given temperature, hydrogen-ion concentration, and ionic strength, but the variations in this ratio from one experiment to another are fairly large. However, $k_2/k_{-1}$ values obtained in this way appear to be very sensitive to small errors in finding the reactant concentrations towards the end of the reaction. We have therefore assumed that the $k_2/k_{-1}$ value found at low initial concentrations of iron(III) should hold at higher concentrations, and we record for each experiment the $k_1$ value found with this assumption, and the percentage of reaction for which the corresponding plots are linear. The constancy of the $k_1$ values is further improved, and even in the most unfavourable cases linear plots are obtained up to 83% reaction. As examples of the various types of plot, Fig. 2 shows for experiment $Q$ the simple second-order plot, the best straight line obtained by using the full equation (ii), and the plot obtained by using the $k_2/k_{-1}$ value found at low initial concentrations of iron(III) (curve I).

In Fig. 3 are plotted iron(II) concentrations at different times for $Q$ and $Q'$; these experiments were similar in all respects except that one was carried out with de-aerated solutions under nitrogen, and the other in air. The corresponding reaction curve for experiment $L$, with a much lower initial concentration of iron(III), is also plotted. From the $k_1$ and $k_2/k_{-1}$ values deduced from $L$, the iron(II) concentrations at different times in

the first two experiments can be calculated, and the corresponding reaction curve is shown as the full line in Fig. 3. This agreement between the experimental and the calculated reaction curves for experiments $Q$ and $Q'$ is also found for other experiments at high initial concentrations of iron(III). This gives further indication that, within experimental error, single values of $k_1$ and $k_2/k_{-1}$ hold for all experiments at a given temperature, hydrogen-ion concentration, and ionic strength.

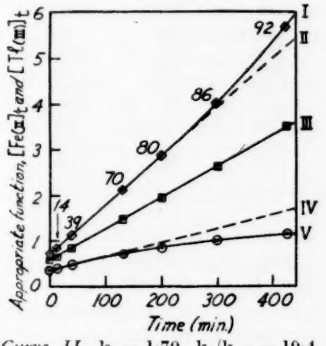
The alternative mechanism involving a 2-electron transfer first step with the formation of iron(IV) as an intermediate leads to a dependence of rate upon concentrations of the form :

$$-\mathrm{d[Fe(II)]}/\mathrm{d}t = 2k_3k_4[\mathrm{Fe(II)}]^2[\mathrm{Tl(III)}]/\{k_4[\mathrm{Fe(II)}] + k_{-3}[\mathrm{Tl(I)}]\} \quad . \quad . \quad \text{(iii)}$$

where $k_3$ and $k_{-3}$ are respectively the velocity constants for the forward and reverse reactions $\mathrm{Fe(II)} + \mathrm{Tl(III)} \rightleftharpoons \mathrm{Fe(IV)} + \mathrm{Tl(I)}$, and $k_4$ is the velocity constant for the reaction $\mathrm{Fe(IV)} + \mathrm{Fe(II)} \longrightarrow 2\mathrm{Fe(III)}$.

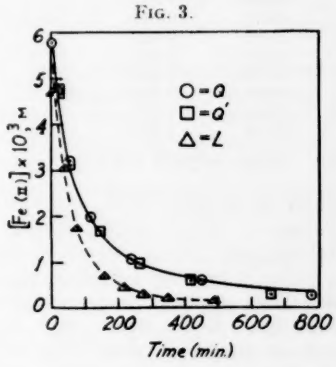
Since we observed no retarding effect of thallium(I) upon the rate of reaction, $k_4$ must

FIG. 2.




*Curve II*, $k_1 = 1{\cdot}70$, $k_2/k_{-1} = 19{\cdot}4$. *Curve III*, $k_1 = 1{\cdot}51$, *best line*. *Curve IV*, $k_1 = 1{\cdot}14$. *Curve V*, *simple second-order plot*. *The numbers above curve I represent reaction*, %.

FIG. 3.




be very much larger than $k_{-3}$ if this mechanism occurs to any extent, and in this case its contribution to the rate of removal of iron(II) would be :

$$-\mathrm{d[Fe(II)]}/\mathrm{d}t = 2k_3[\mathrm{Fe(II)}][\mathrm{Tl(III)}] \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

We conclude, however, that equation (ii) without an extra term in $k_3$ is in accord with the experimental results, and therefore we consider that these results provide good evidence that reaction proceeds through steps (1) and its reverse and (2), and that the alternative mechanism is unimportant.

*Dependence of the Velocity Constants on Hydrogen-ion Concentration.*—In Table 3 we list data from experiments at various hydrogen-ion concentrations between 0·4M and 2·8M. The concentrations of reactants are about twice as large as generally used in Johnson's experiments. Our values for $k_1$ have been analysed in the same way as his $k$ values, and we conclude, similarly, that this constant can be expressed by

$$K_1(k_1' + k_1''K_2/[\mathrm{H^+}])/(K_1 + [\mathrm{H^+}])$$

Here $k_1'$ and $k_1''$ correspond to Johnson's $k_1$ and $k_2$, respectively, $K_1$, the first hydrolysis constant of $\mathrm{Tl^{+++}}$, is taken as 6·4 mole l.$^{-1}$, and $K_2$ is its second hydrolysis constant (see Johnson, *loc. cit.*). We find $k_1' = 0{\cdot}85 \pm 0{\cdot}02$ mole$^{-1}$ l. min.$^{-1}$ (Johnson finds $k_1 = 0{\cdot}84$), and $k_1''K_2 = 0{\cdot}82 \pm 0{\cdot}02$ min.$^{-1}$ (Johnson finds $k_2K_2 = 0{\cdot}74$). At the low initial concentrations of iron(III) in these and Johnson's experiments there is not more than

2% difference between corrected $k_1$ values and those taken from the initial slope of the simple second-order plot; hence the reasonable degree of agreement found between his values and ours. Since curvature was only apparent in his simple second-order plots after 60—70% of reaction, it is probable that under conditions where we have not done parallel experiments the values of $k$ found from the initial gradients of his plots are also good values for $k_1$.

With regard to Johnson's conclusions about the nature of the reacting species, the form of the variation of $k_1$ with the hydrogen-ion concentration indicates only that the reaction between thallium(III) and iron(II) can take two paths involving the formation of two transition complexes, the one including $Tl^{+++}$, $Fe^{++}$, and $OH^-$, and the other including $Tl^{+++}$, $Fe^{++}$, and $2OH^-$. Thus, for example, reaction between $Tl^{+++}$ and $FeOH^+$ cannot be distinguished from that between $TlOH^{++}$ and $Fe^{++}$, and it is incorrect therefore to identify $k_1'$ and $k_1''$ with reactions between specific ions.

TABLE 3.

| Expt. | Initial concns., M × $10^3$ Fe(II) | Fe(III) | [$H^+$], M | Best values, $k_1$ | $k_2/k_{-1}$ | % linear | Simple second-order plot: $k_1$ | % linear |
|---|---|---|---|---|---|---|---|---|
| *R* | 8·62 | 1·357 | 0·40 | 2·74 | 16·2 | 96 | 2·80 | 45 |
| *S* | 9·06 | 0·913 | 0·668 | 1·89 | 23·6 | 98 | 1·86 | 60 |
| *T* | 9·06 | 0·913 | 1·00 | 1·45 | 30·8 | 98 | 1·43 | 60 |
| *U* | 9·06 | 0·913 | 1·50 | 1·10 | 45·2 | 98 | 1·10 | 65 |
| *V* | 8·73 | 1·245 | 1·50 | 1·09 | 45·2 | 96 | 1·09 | 70 |
| *W* | 9·06 | 0·913 | 2·00 | 0·94 | 50·0 | 98 | 0·92 | 75 |
| *X* | 8·62 | 1·357 | 2·40 | 0·86 | 58·2 | 95 | 0·86 | 60 |
| *Y* | 8·73 | 1·245 | 2·80 | 0·82 | 63·8 | 98 | 0·82 | 55 |

ionic strength = 3·00; [Tl(I)] = $2·95 \times 10^{-4}$M; [Tl(III)] = $1·018 \times 10^{-2}$M.

In Table 3, values of $k_2/k_{-1}$ are also tabulated for each experiment. The accuracy of these values is about ±6%; within this limit the dependence upon hydrogen-ion concentration can be expressed as $k_{-1}/k_2 = 0·0215/[H^+] + 0·0090$. If it is assumed that $k_{-1}$ is likely to show a similar type of dependence on the hydrogen-ion concentration to $k_1$, since both apply to reaction between a tervalent and a bivalent metal ion, then

$$k_{-1} = (k_{-1}' + k_{-1}''/[H^+])/(K_3 + [H^+])$$

$K_3$, by analogy with the forward reaction, is the first hydrolysis constant of $Fe^{+++}$, and if it is small compared with the hydrogen-ion concentration, the above equation becomes $k_{-1} = (k_{-1}' + k_{-1}''/[H^+])/[H^+]$. The form of the experimental dependence of $k_{-1}/k_2$ on the hydrogen-ion concentration can now be obtained if it is assumed that the rate of the reaction between thallium(II) and iron(II) depends inversely on the hydrogen-ion concentration, *i.e.*, if $k_2 \propto 1/[H^+]$. There are of course numerous ways in which $k_{-1}$ and $k_2$ can vary with [$H^+$] and give the observed dependence of $k_{-1}/k_2$; the above assumptions seem to be the most reasonable. The accuracy with which the values of $k_2/k_{-1}$ have been determined is such that it is permissible to neglect $K_3$ compared with [$H^+$] provided $K_3 \gg 0·1$ mole $l.^{-1}$. This constant was determined by a spectrophotometric method at 25° and ionic strength 3·00, and shown to be approximately 0·003 mole $l.^{-1}$.

## EXPERIMENTAL

*Stock Solutions.—Thallium*(III) *perchlorate.* Thallium(I) chloride was precipitated from " AnalaR " thallium(I) sulphate, and recrystallised from water. It was oxidised in suspension in dilute hydrochloric acid by potassium bromate, the solution filtered, and thallium(III) oxide precipitated with ammonia. This precipitate was washed free from chloride ions, and dissolved in excess of 60% " AnalaR " perchloric acid, and the solution filtered and diluted with water to 2M with respect to acid. Total thallium in the solution was determined by reduction of thallium(III) by sulphur dioxide to thallium(I), followed by titration against potassium iodate in 6M-hydrochloric acid solution. Thallium(I) present initially was found by a similar titration on the original solution; thallium(III) was found by difference. The solution was standardised at intervals, but was fairly stable.

Thallium(I) perchlorate was obtained from pure thallium(I) nitrate by fuming with excess of 60% perchloric acid, and recrystallised three times from water. A stock solution was made up by weight, and checked by titration against potassium iodate.

Iron(II) perchlorate solution in dilute perchloric acid was prepared by dissolving Hilger's " H.H.P. " iron turnings in excess of dilute perchloric acid. The solution was frequently standardised against potassium dichromate, with *N*-phenylanthranilic acid as indicator. Iron(III) present was obtained by subtracting the iron(II) concentration from that of total iron, calculated from the weight of metal used.

Iron(III) perchlorate solution was prepared from the iron(II) perchlorate solution by oxidation with excess of concentrated hydrogen peroxide solution.

Sodium perchlorate solution was prepared by neutralising " AnalaR " perchloric acid with " AnalaR " sodium hydroxide and filtering.

*Procedure.*—The reaction was followed by determining the iron(II) concentration in the reaction mixture at intervals. Samples of the reaction mixture were quenched in excess of cerium(IV) ammonium sulphate solution, followed by back-titration to the ferroin end-point with iron(II) ammonium sulphate solution. 0·01M- and 0·004M-Solutions of these reagents were used as required and were prepared by dilution from 0·1M-stock solutions. The diluted iron(II) solutions were standardised potentiometrically against a standard potassium dichromate solution, and the corresponding cerium(IV) solutions were then standardised against these iron(II) solutions by use of ferroin. These diluted iron(II) and cerium(IV) solutions slowly decreased in strength and were frequently restandardised.

The accuracy of the determination of iron(II) in the reaction samples was determined in independent experiments under similar experimental conditions. It was shown that the presence of thallium(I) and thallium(III) does not affect the ferroin end-point when the excess of cerium(IV) is titrated with iron(II). The end-point was improved by addition of sulphuric acid to make the solution 0·5M in this acid before commencement of the back-titration; the ferroin indicator also seemed to be more stable when this amount of sulphuric acid was used. In such solutions a very slow oxidation of thallium(I) by cerium(IV) occurs. The excess of cerium(IV) was therefore kept small, and the reaction sample back-titrated within 10 min. of being quenched. Under these conditions errors were as stated below except in experiments at high ($\geqslant 10^{-2}$M) thallium(I) concentrations, where the appropriate first- or second-order plots were similar to those for the corresponding experiments at low thallium(I) concentrations but showed an apparent decrease in rate after 85—90% of reaction. This was consistent with the expected over-consumption of cerium(IV) owing to the oxidation of thallium(I). It was concluded that, with the exception mentioned, the concentration of iron(II) in the reaction solution could be determined to $\pm 10^{-5}$M, an error of about $\pm 20\%$ of the total iron(II) concentration at 98% reaction. Systematic errors, if present, were within these error limits. In most kinetic experiments a titration was taken at 98—100% reaction. Even in the presence of large concentrations of the products the reaction appeared to go to completion.

All kinetic experiments were done at 25·0° ± 0·05° in 500-ml. glass-stoppered flasks. The initial volume of the reaction solutions was from 100 to 250 ml., and 10, 20, or 25 ml. samples were taken as appropriate. Several experiments were repeated under nitrogen, de-aerated solutions being used; no significant difference was observed between these experiments and duplicates carried out in air. An experiment in absence of light gave results identical with those of a duplicate in daylight. Most experiments were therefore done in air and without precautions to keep out light. In all cases sodium perchlorate solution was used to make up the ionic strength to the values quoted. The amount of chloride ion in the reaction solutions at ionic strength = 3·00 was not greater than $2{\cdot}5 \times 10^{-4}$M; experiments showed that concentrations of chloride ion of this magnitude have negligible effects on the rate of reaction. At chloride-ion concentrations of the same order as the reactant concentrations we observed similar retardation phenomena to those described by Forchheimer and Epple (*loc. cit.*), and we believe their explanation to be essentially correct.

We thank Mr. J. C. Stocks for assistance in the early stages of this investigation.

THE UNIVERSITY, MANCHESTER, 13. [*Received, January* 31*st*, 1953.]

## 606. *Partition Coefficients of Some Amidines.*

By J. Cymerman-Craig, (Miss) M. J. Parker, and (Miss) P. Woodhouse.

Partition coefficients between liquid paraffin and water at pH 7·2 have been measured for some twenty *N*-4-diphenylylamidines, *p*-phenylbenzamidines, and related compounds. Ionisation constants for ten *p*-phenylbenzamidines have been determined in 50% alcohol, and the results are discussed.

As part of an investigation of the effect of variation in lipoid solubility and basic strength on antituberculous activity, two series of compounds containing the diphenyl structure, *viz.*, *N*-4-diphenylylamidines (II) and *p*-phenylbenzamidines (I), were prepared (Bauer and Cymerman, *J.*, 1950, 1826, 2078). The ionisation constants of the former series have been reported by Carswell, Cymerman, and Lyons (*J.*, 1952, 430), and the determination of the basic strengths of the ten substances of the latter series, and the lipoid–water partition coefficients of sixteen bases belonging to both series, and of four related aromatic amines, are now described.

*Method.*—The partition coefficients between liquid paraffin (B.P. 1932) and aqueous phosphate buffer at pH 7·2 (the physiological pH) were determined at 20° ± 2° by the spectrophotometric method of Cymerman-Craig and Diamantis (*J.*, 1953, 1619), and the values of the apparent partition coefficient ($k'$) are given in Tables 1 and 2, together with the wave-length of the absorption maximum.

For five amidines, water-solubility of the hydrochlorides was so low that a suitable aqueous solution (*i.e.*, one of optical density not less than 0·2) could not be obtained, and so measurement was impossible. In the twenty compounds measured, the partition coefficients range from 0·075 to 126 according to the nature of the lipophilic group.

In view of the unexpectedly low values of $k'$ found for some compounds of type (I) (Table 1), their p$K_a$ values were determined by potentiometric titration in 50% aqueous-alcoholic solution at 20° ± 1° by the method described by Carswell, Cymerman, and Lyons (*loc. cit.*), and the results are given in Table 1.

For the amidines, the hydrochlorides were titrated with 50% aqueous-alcoholic N/20-sodium hydroxide, and the base 2 : 4′-diphenylylbenziminazole was titrated with 50% aqueous-ethanolic N/20-hydrochloric acid. Results were corrected for hydrogen- and hydroxyl-ion concentration where necessary.

Owing to the low solubility of *N*-*p*-chlorophenyl-*p*-phenylbenzamidine in 50% ethanol, its potentiometric titration was carried out in 67% ethanol, and the p$K_a$ in 50% aqueous-alcoholic solution was determined by measurement of the pH at the exact half-neutralisation point.

It has been shown (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472; Albert and Goldacre, *J.*, 1946, 706) that the temperature coefficient of basic strength is of the order of −0·01 to −0·03 unit per degree; our results, although therefore mainly of qualitative interest, do provide an interpretation of the apparently anomalous partition coefficients ($k'$) found for the compounds recorded in Table 1.

*Discussion.*—Benzamidine has p$K_a$ 11·23 in 50% alcohol (Baxter and Cymerman-Craig, *J.*, 1953, 1490), and in *p*-phenylbenzamidine (Table 1) the $+E$ effect of the additional phenyl group is seen to reduce the basic strength by 0·14 unit. The introduction of an alkyl residue R on the amino-nitrogen atom of the amidine group [Table 1 (*a*)] has a base-weakening effect ($\Delta pK$ − 0·36 and −0·33 unit) when R is *n*-butyl and *cyclo*hexyl respectively. Clearly, the destruction of the equivalence of the two structures contributing to the amidinium ion has a base-weakening effect greater than the base-strengthening ($-I$) effect of the additional alkyl group. That the presence of two $-I$ groups is capable of offsetting this drop in p$K_a$ is shown by *NN*-di-*n*-butylbenzamidine (Lorz and Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992) which has p$K_a$ 11·27 in 50% methanol and by the similar effect observed in the *N*-methyl-substituted guanidines (Angyal and Warburton, *J.*, 1951, 2492).

Series (*b*) (I; R = aryl) shows the $+E$ effect of the phenyl residue together with the effect of the *p*-substituent attached to the phenyl group. The p$K_a$ (7·95) of the compound (I; R = Ph) is seen to be close to that (8·10) of the isomer (II; R = Ph) (Carswell, Cymerman, and Lyons, *loc. cit.*), as expected. The p$K_a$'s of the *p*-alkoxy-substituted compounds are in accord with the $-E$ effect of these substituents, and the very small difference between the *p*-ethoxy- and *p*-*n*-butoxy-substituted compounds is in agreement with the close resemblance between the p$K_a$ values of the corresponding *p*-alkoxybenzoic acids (Cavill, Gibson, and Nyholm, *J.*, 1949, 2466). The *p*-chloro-group shows the expected base-weakening effect.

TABLE 1. *Ionisation and partition coefficients of* p-*phenylbenzamidines*, *p*-Ph·$C_6H_4$·C(:NH)·NHR (I).

| | R | p$K_a$ [1] at 20° ± 1° | $k'$ at 20° ± 2° | $\lambda_{max.}$, mμ |
|---|---|---|---|---|
| (*a*) | H | 11·09 | 0·075 | 273 |
| | *n*-$C_4H_9$ | 10·73 | 0·20 | 273 |
| | *cyclo*Hexyl | 10·76 | 0·21 | 269 |
| | (2-4′-Diphenylyl-4 : 5-dihydroglyoxaline [4]) | 9·29 | 0·11 | 280 |
| (*b*) | Ph [6] | 7·95 | 6·4 | 278 |
| | *p*-Ethoxyphenyl | 8·12 | 6·7 | 278 |
| | *p*-*n*-Butoxyphenyl [7] | 8·10 | — [5] | — |
| | *p*-Chlorophenyl [8] | 7·65 [3] | — [5] | — |
| | | 7·74 [3] | | |
| | *p*-*N*-Piperidinophenyl | 8·00 | 7·5 | 278 |
| | (2-4′-Diphenylylbenziminazole) | 3·64 | — [5] | — |

[1] In 50% alcohol. [2] In 67% alcohol by potentiometric titration. [3] In 50% alcohol from half-neutralisation point. [4] The *hydrochloride* formed needles from methanol–ether, m. p. 318° (Found: N, 10·65. $C_{15}H_{14}N_2$,HCl requires N, 10·8%). [5] Measurement impossible owing to insolubility in water. [6] The *hydrochloride* formed plates, m. p. 210—211°, from alcohol–ether (Found: N, 9·45. $C_{19}H_{16}N_2$,HCl requires N, 9·1%). [7] The *hydrochloride* had m. p. 213° (Found: 7·4. $C_{23}H_{24}ON_2$,HCl requires N, 7·35%). [8] The *hydrochloride* had m. p. 224° (Found: N, 8·25. $C_{19}H_{15}N_2Cl$,HCl requires N, 8·15%).

TABLE 2. *Partition coefficients of* N-4-*diphenylylamidines*, *p*-Ph·$C_6H_4$·NH·CR(:NH) (II) *and aminodiphenyls at* 20° ± 2°.

| | R | $k'$ | $\lambda_{max.}$, mμ | | R | $k'$ | $\lambda_{max.}$, mμ |
|---|---|---|---|---|---|---|---|
| (*a*) | Me | 0·18 | 259 | (*b*) | Ph | 7·0 | 263 |
| | *n*-$C_5H_{11}$ | 1·9 | 259 | | *p*-Ethoxyphenyl | 19·0 | 275 |
| | *n*-$C_7H_{15}$ | 26·0 | 259 | | 3 : 4-Dimethoxyphenyl | 33·0 | 272 |
| | *n*-$C_{16}H_{33}$ [1] | — [2] | — | | *p*-Chlorophenyl | — [2] | — |
| | *cyclo*Pent-1-enyl | 3·4 | 254 | | *p*-Ethoxycarbonylphenyl | — [2] | — |
| | *cyclo*Hex-1-enyl | 7·5 | 259 | | | | |
| | *cyclo*Hexyl | 7·6 | 260 | (*c*) | 4-Aminodiphenyl | 55 | 272 |
| | | | | | 3-Aminodiphenyl | 47 | 230 |
| | | | | | 2-Aminodiphenyl | 126 | 221 |
| | | | | | Aniline | 0·75 | 230 |

[1] The *hydrochloride* formed waxy plates from benzene–ether, m. p. 167—168° (Found: C, 75·95; H, 9·5. $C_{29}H_{44}N_2$,HCl requires C, 76·2; H, 9·85%). [2] Measurement impossible owing to insolubility in water.

The cyclic analogue 2-4′-diphenylyl-4 : 5-dihydroglyoxaline is seen to be a strong base, although almost 1·5 p$K$ units weaker than the open-chain *N*-alkyl-*p*-phenylbenzamidines. The high basic strength of glyoxaline (p$K_a$ 7·03 at 20° in water: Albert, Goldacre, and Phillips, *J.*, 1948, 2240) compared with that of pyridine or pyrimidine is probably due to the symmetry of the glyoxalinium cation (cf. Schofield, *Quart. Reviews*, 1950, **4**, 382) in spite of the electron-withdrawing effect of the olefinic linkage in the ring. It can be presumed that dihydroglyoxaline (the p$K_a$ of which has apparently not been measured) would be a still stronger base, since it could be regarded as a cyclised *NN*′-dimethylformamidine, and the high p$K_a$ of the diphenylyl derivative is thus consistent with the expected results. Its lower homologue, 4 : 5-dihydro-2-phenylglyoxaline, is described as a " strong base " (Forssel, *Ber.*, 1892, **25**, 2135). In benziminazole the additional mesomeric effect of the benzo-group has reduced the p$K_a$ to 5·53 in water at 20° (Albert, Goldacre, and Phillips, *loc. cit.*), and the further reduction to 3·64 in the case of the diphenylyl derivative is again in accord with the $+E$ effect of the aryl group.

The oil–water partition coefficients of the *N*-4-diphenylylamidines (II) (Table 2) follow the accepted order of lipophilic nature of the group R, whereas in the corresponding results for the *p*-phenylbenzamidines (I) (Table 1) the aliphatic group (*a*) is seen to have very much lower values for $k'$ than their isomers (II; R = aliphatic) in Table 2 (*a*). This apparent anomaly is, however, accounted for by the higher $pK_a$ (9·3—11) of the substances in section (*a*) of Table 1, whereas those in Table 2 (*a*) have $pK_a$ 8·6—9·3. Since the measured partition coefficient ($k'$) is related to the true partition coefficient ($k$, where $k = [B]_0/[B]_w$, $[B]_0$ and $[B]_w$ being the concentrations of the undissociated base in the two phases) as shown in the equation below (Cymerman-Craig and Diamantis, *loc. cit.*), it follows that at pH 7·2 the ratio $k/k'$ for a base of $pK_a$ 10·2 will be ten times as great as for a base of $pK_a$ 9·2. This explanation is borne out by the similarity of the values of $k'$ for compounds of comparable $pK_a$ in section (*b*) of Tables 1 and 2. The high values of $k'$ for the isomeric aminodiphenyls [Table 2 (*c*)] compared with that of aniline are in accord with the fact that here all four compounds have $pK_a$ not exceeding 4·5, so that $k = k'$ in the equation $k/k' = 1 + \text{antilog}\ (pK_a - \text{pH})$.

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## 607. *Researches on Acetylenic Compounds. Part XL.* The Synthesis of Some ω-Acetylenic Acids.*

By G. Eglinton and M. C. Whiting.

Syntheses, by convenient routes, of a number of straight-chain aliphatic acids possessing terminal acetylenic groups are described. Known primary acetylenic alcohols were used as starting materials.

A range of acids of type (I) was required for an investigation of prototropic rearrangements in molecules containing a terminal acetylenic linkage and another functional group, not necessarily in close proximity. The synthetical methods employed were based on chain-extension from primary acetylenic alcohols. The work described in Parts XXVII (Eglinton and Whiting, *J.*, 1950, 3650) and XXXVIII (Eglinton, Jones, and Whiting, *J.*, 1952, 2873) arose from the need for intermediates in the present syntheses.

$HC{\equiv}C{\cdot}[CH_2]_n{\cdot}CO_2H$ (I) $\qquad$ $HC{\equiv}C{\cdot}[CH_2]_n{\cdot}CH_2{\cdot}OH$ (II)

The first member (excluding propiolic acid) is readily available (Heilbron, Jones, and Sondheimer, *J.*, 1949, 604). The acid (I; $n = 2$) was first prepared, in very low yield, by Perkin and Simonsen (*J.*, 1907, **91**, 816); it was also obtained, again by an unsatisfactory method, by Schjånberg (*Ber.*, 1938, **71**, 569). As an attempt at improvement, prop-2-ynyl bromide was treated with sodiomalonic ester, and a mixture of the mono- and di-substituted malonic esters with unchanged malonic ester was readily obtained. Careful fractionation under reduced pressure gave a 40% yield of the monopropynyl ester; hydrolysis and decarboxylation then proceeded normally and in good yield. Alternatively, prop-2-ynyl bromide was found to react with β-dimethylamino- or β-diethylamino-crotonic ester to give an ether-insoluble quaternary salt, which was hydrolysed by warm water to the pure monosubstituted acetoacetic ester in excellent overall yield. The advantages of this method over the normal acetoacetic ester synthesis are obvious; they depend on the important fact that the proton-exchange equilibrium between (III) and (IV) is not readily established (cf. Robinson, *J.*, 1916, 1038). This selective alkylation is, unfortunately,

* Part XXXIX, *J.*, 1952, 2873.

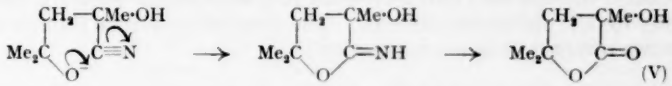
applicable only to halides of unusual reactivity, since attempts to employ 4-bromobut-1-yne or the corresponding iodide or toluene-*p*-sulphonate were unsuccessful.

$$\underset{}{R'Br} + \underset{(III)}{Me_2N{\cdot}CMe{:}CH{\cdot}CO_2R} \longrightarrow \underset{(IV)}{Me_2\overset{+}{N}{:}CMe{\cdot}CHR'{\cdot}CO_2R\ \ Br^-}$$

The monopropynylacetoacetic ester was readily hydrolysed to (I; $n = 2$) and to hex-5-yn-2-one, though the yield of the former was low. At about this time, however, a very convenient synthesis of pent-4-yn-1-ol (II; $n = 2$) was devised (Part XXXVIII, *loc. cit.*), and direct oxidation of this alcohol with chromic acid in aqueous solution gave the best route to (I; $n = 2$), a 50% yield being obtained.

For the synthesis of pent-4-yne-1-carboxylic acid (I; $n = 3$), which at the time was unknown, three methods were investigated. The first, involving the interaction of but-3-ynyl toluene-*p*-sulphonate (Part XXVII, *loc. cit.*) with sodiomalonic ester, gave vinylacetylene as the main product. Hydrolysis of the small non-volatile fraction did, however, give a 3·5% yield of the expected monosubstituted malonic acid, which was smoothly decarboxylated to (I; $n = 3$). The use of 4-iodobut-1-yne in place of the toluene-*p*-sulphonate increased the yield of the butynylmalonic ester only to 7%. As an alternative route, pent-4-ynyl toluene-*p*-sulphonate and potassium cyanide in alcohol gave the expected nitrile in 75% yield. Controlled hydrolysis of the nitrile led to (I; $n = 3$) in excellent yield.

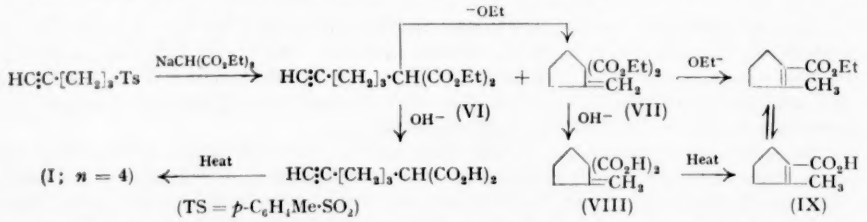
When acetone was used instead of alcohol as solvent for the preparation of the nitrile, the yield fell to 60%, and a by-product (V) was isolated in considerable quantity; this had been previously obtained *inter al.* from diacetone alcohol *via* the cyanohydrin by Henze, Thompson, and Speer (*J. Org. Chem.*, 1943, **8**, 17). Although hydrolysis of the acetylenic nitrile was negligible, that of the hydroxy-cyanohydrin proceeded readily, presumably facilitated by the proximity of the reacting centres:




Pent-4-yne-1-carboxylic acid was also obtained by direct oxidation of hex-5-yn-1-ol (Part XXXVIII, *loc. cit.*), giving a good three-stage synthesis from tetrahydro-2-pyranylmethanol.

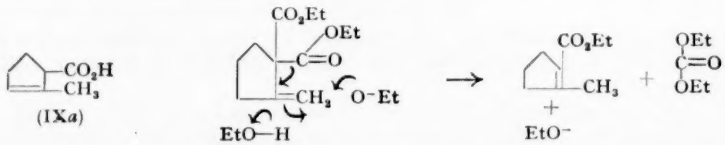
The obvious method for the synthesis of hex-5-yne-1-carboxylic acid (I; $n = 4$) involved the interaction of pent-4-ynyl toluene-*p*-sulphonate with sodiomalonic ester. Unexpectedly the product was a complex mixture. Provided that an appreciable excess of malonic ester over sodium ethoxide was used, this mixture could be separated into (*a*) a fraction containing two isomeric esters, $C_{12}H_{18}O_4$, discussed below, (*b*) diethyl undeca-1 : 10-diyne-6 : 6-dicarboxylate, the expected disubstitution product, and (*c*) a little unchanged starting material. The two lower boiling esters could only be partly separated by distillation, but hydrolysis of concentrates gave two isomeric acids, $C_8H_{10}O_4$. One of these, m. p. 94—95° (decomp.), obtained from the higher-boiling ester fraction, gave an acid, m. p. 22—22·5°, on decarboxylation. This was clearly (I; $n = 4$), since it showed no light absorption of high intensity above 2200 Å, absorbed two molecular proportions of hydrogen to form *n*-heptanoic acid, and was converted readily into an ester which gave a silver derivative. The other, m. p. 120—130° (decomp.), gave an acid, m. p. 131—132°, on decarboxylation to which the structure (IX) was assigned on the basis of (*a*) its absorption maximum at 2300 Å ($\varepsilon$ 10,300), (*b*) its uptake of only one molecular proportion of hydrogen, to give a liquid acid of which the physical constants and the melting-point of the amide agreed with those recorded for 2-methyl*cyclo*pentane-1-carboxylic acid, and (*c*) the known existence of two acids, m. p.s 130° and 131°, to which structure (IX*a*) had been ascribed on evidence which did not exclude (IX) (Haworth and Perkin, *J.*, 1908, **93**, 584; Wallach and Ollichmacher, *Annalen*, 1899, **305**, 225). More recently (IX) has been prepared by Shimizu (*Chem. Abs.*, 1950, **44**, 8868) who reported m. p. 132° and rigorously proved the structure of his product.

Given the structures of (VI), the necessary precursor of (I; $n = 4$), and (IX), those of the intermediates (VII and VIII) followed, and were confirmed by the transparency of (VIII) above 2200 Å, and the presence of a strong band at 900 cm.$^{-1}$ ($>C{:}CH_2$) in the infrared spectrum of (VII) (personal communication from the late Dr. H. P. Koch); (VII) also




gave a 22% yield of formaldehyde on ozonolysis. The refluxing of a solution of (VI) in ethanol containing a little sodium ethoxide gave (VII), suggesting that the reaction involves addition of the $-\bar{C}(CO_2Et)_2$ moiety to the acetylenic linkage; since (VII) was never obtained free from (VI), an equilibrium between the two esters is not excluded. Nucleophilic additions to acetylenic compounds, especially acetylene itself, are now known to take place much more readily than with the corresponding olefins. Addition of malonic ester residues has not been reported, and unsuccessful attempts were therefore made to carry out such reactions with hex-1-yne and diethyl malonate and methylmalonate, temperatures considerably higher than those used in the cyclisation of (VI) being without effect. Clearly an intramolecular environment here favours cyclisation.

When (VI) was treated with more than one equivalent of sodium ethoxide in refluxing ethanol, a lower-boiling product resulted which consisted essentially of the ethyl ester of (IX), also obtained (though with difficulty) from (IX) in ethanolic sulphuric acid; hydrolysis of the ester to (IX) also proved difficult. The decarbethoxylation reaction is a variant of the well-known reversed Claisen condensation :




A small quantity of the ethyl ester of (I; $n = 4$) was, however, also present, apparently as the result of a reversed Claisen condensation with (VI) preceding cyclisation; it was recognised by the detection of a substance containing an ethynyl grouping in the crude ethyl 2-methyl*cyclo*pentene-1-carboxylate.

In collaboration with Mr. G. H. Whitham it was found that the mixed malonic acids, obtained by hydrolysis of the $C_{12}$ esters (VI) and (VII), could be decarboxylated in *N*-hydrochloric acid at 100°, and that (IX) then separated almost quantitatively at 0°. Extraction and distillation gave (I; $n = 4$) in 44% overall yield from pent-4-ynyl toluene-*p*-sulphonate.

An attempt was made to determine the structural features required for the novel cyclisation described above. Diethyl hept-6-yne-1 : 1-dicarboxylate was obtained from hex-5-ynyl toluene-*p*-sulphonate without difficulty but would not cyclise. The condensation product from pent-4-ynyl toluene-*p*-sulphonate and sodioacetoacetic ester proved to be the straight chain product, and on warming with sodium ethoxide in ethanol gave mainly low-boiling decarbethoxylated and deacetylated products from which, however, a small quantity of (IX) was obtained after hydrolysis. On the other hand, the ester of (I; $n = 4$) itself did not cyclise under the normal conditions, while very vigorous alkaline treatment would, of course, result in prototropic migration of the triple bond. Thus the conditions for this reaction apparently include a chain of three methylene groups between an acetylenic linkage and a pseudo-acidic centre comparable in strength with $-CH(CO_2Et)_2$.

Hept-6-yne-1-carboxylic acid (I; $n = 5$) was readily prepared by hydrolysis and decarboxylation of diethyl hept-6-yne-1 : 1-dicarboxylate. It had previously been obtained by Newman and Wotiz (*J. Amer. Chem. Soc.*, 1949, **71**, 1293).

Of the remaining ω-acetylenic acids, two have been prepared from the corresponding ethylenes by bromination and dehydrobromination (dec-9-yne-1-carboxylic acid, *inter al.* by Lauer and Gensler, *J. Amer. Chem. Soc.*, 1945, **67**, 1171 : nonadec-18-yne-1-carboxylic acid by Stenhagen, *Arkiv Kemi*, 1949, **1**, 99). The first member (I; $n = 1$) of the series is unusually sensitive to alkalis, (I; $n = 2$) is hydrated more readily than most acetylenic compounds in acidic solution, and the two acids (I; $n = 2$ and 3) are both isomerised in boiling 20—40% sodium hydroxide solution. With these exceptions, to be discussed later, ω-acetylenic acids can be esterified and recovered from esters, etc., in the usual manner provided that exceptionally drastic conditions are avoided.

## Experimental

Unless otherwise specified, light petroleum refers to the fraction of b. p. 40—60°. Melting-points denoted m. p. (K) were determined on the Kofler block. Light-absorption data were obtained in alcoholic solution. The ethynyl group estimations were carried out by a method developed in the laboratories of Messrs. Glaxo Ltd. (personal communication from Dr. R. M. Evans) : the sample (*ca.* 0·15 g.) was dissolved in ethanol (35 c.c.) containing 6 drops of a solution of methyl red (0·1 g.) and methylene blue (0·05 g.) in ethanol (100 c.c.); aqueous silver nitrate solution (10%; 12·5 c.c.) was added, and the mixture was titrated to a blue-grey end point with sodium hydroxide solution (NaOH ≡ ·C:CH).

The preparation of the primary acetylenic alcohols and their toluene-*p*-sulphonates was described in Parts XXVII and XXXVIII (*locc. cit.*).

*Diethyl But-3-yne-1 : 1-dicarboxylate.*—Prop-2-ynyl bromide (29·5 g.) was slowly added to an alcoholic suspension of ethyl sodiomalonate [from sodium (5·9 g.), ethyl alcohol (100 c.c.), and ethyl malonate (40 g.)], and the mixture was stirred for 16 hr. and then poured into water. After isolation with ether, the product was distilled through a 30-cm. Fenske column into three main fractions : (*a*) ethyl malonate (7 g.); (*b*) diethyl but-3-yne-1 : 1-dicarboxylate (20 g., 40%), b. p. 109·5°/13 mm., $n_D^{20}$ 1·4384 (Found : C, 60·5; H, 7·2. Calc. for $C_{10}H_{14}O_4$ : C, 60·6; H, 7·1%) (Perkin and Simonsen, *J.*, 1907, 816, 840, give b. p. 129°/22 mm.); and (*c*) diethyl hepta-1 : 6-diyne-4 : 4-dicarboxylate (7 g.), b. p. 122—126°/13 mm., m. p. 45°, $n_D^{20}$ 1·4510 (supercooled liquid) (Brockmühl, Schwabe, and Ehrhart, *Chem. Zent.*, 1928, II, 1823; 1931, II, 742, give m. p. 45·5°).

*But-3-yne-1 : 1-dicarboxylic Acid.*—Diethyl but-3-yne-1 : 1-dicarboxylate (2 g.) was shaken with a solution of potassium hydroxide (1·5 g.) in water (1 c.c.), and the resultant solution set aside for 24 hr. The acid, after isolation with ether, was obtained as deliquescent needles (540 mg., 38%), m. p. 139° (decomp.) after recrystallisation from ether–light petroleum (b. p. 60—80°) [Perkin and Simonsen (*loc. cit.*) give m. p. 139° (decomp.)]. Decarboxylation at 150° of a small sample gave but-3-yne-1-carboxylic acid (I; $n = 2$), m. p. 56—57° [Perkin and Simonsen (*loc. cit.*) record m. p. 57°].

*Ethyl 2-Oxohex-5-yne-3-carboxylate.*—(*a*) A solution of prop-2-ynyl bromide (39 g.) in dry ether (20 c.c.) was added to a stirred and cooled suspension of ethyl sodioacetoacetate [from sodium (7·3 g.) and ethyl acetoacetate (43 g.)] in dry ethanol (100 c.c.) at such a rate that the temperature did not exceed 30°. After being stirred at 20° for 24 hr., the suspension was filtered and the solvent removed from the filtrate by evaporation. Water was added and the product isolated with ether. Fractionation at high reflux ratio through a 30-cm. Fenske column gave ethyl acetoacetate (4·6 g.), *ethyl 2-oxohex-5-yne-3-carboxylate* (26·3 g., 50%), b. p. 104—105°/16 mm., $n_D^{20}$ 1·4480 (Found : C, 64·5; H, 6·9. $C_9H_{12}O_3$ requires C, 64·2; H, 7·2%), and a fraction (14·5 g.), b. p. 119—127°/16 mm., $n_D^{20}$ 1·4636, which gave a silver derivative and was probably essentially the disubstituted ester.

(*b*) A mixture of ethyl β-dimethylaminocrotonate (3·1 g.; Glickman and Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1019) and prop-2-ynyl bromide (3·0 g.) was set aside at 20° for 3 days. The syrupy quaternary salt, after repeated extraction with dry ether, was hydrolysed by heating it under reflux with water (4 c.c.) for 5 min. The product was isolated with ether and distilled to give the ester (2·85 g., 86%), b. p. 48—49°/0·05 mm., $n_D^{24}$ 1·4450.

(*c*) The use of β-diethylaminocrotonic ester in a similar reaction gave a very hygroscopic crystalline quaternary salt, m. p. *ca.* 118°, in a rather slower reaction. Hydrolysis gave the acetylenic ketone described below.

*Hex-5-yn-2-one.*—Ethyl 2-oxohex-5-yne-3-carboxylate (5·2 g.) was shaken for 16 hr. with a 5% aqueous solution of sodium hydroxide (40 c.c.). The resulting solution was washed with ether and then carefully acidified with dilute sulphuric acid (1 : 1), and the product was isolated with ether. Distillation gave the ketone (1·2 g., 35%), b. p. 76°/85 mm., $n_D^{18}$ 1·4340—1·4355 (Gardner and Perkin, *J.*, 1907, 848, give b. p. 149°/749 mm.). But-3-yne-1-carboxylic acid (0·2 g.), m. p. 55—56°, was isolated from the distillation residue. The ketone semicarbazone had m. p. 135—136°, after crystallisation from methanol (Gardner and Perkin, *loc. cit.*, give m. p. 135—136°). The 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 138—139°, from carbon tetrachloride (Found : C, 52·25; H, 4·4. $C_{12}H_{12}O_4N_4$ requires C, 52·2; H, 4·35%).

*But-3-yne-1-carboxylic Acid* (preparative method).—Chromic acid (6N in 12N-sulphuric acid) (240 c.c.) was added during 1 hr. to a stirred and cooled (below 20°) solution of pent-4-yn-1-ol (28·4 g.) in water (200 c.c.). After 16 hr. the acidic fraction (20 g.) was isolated with ether and crystallised from light petroleum giving lustrous plates (16·4 g., 50%), m. p. (K) 57—58° after recrystallisation from the same solvent. *Pent-4-ynyl but-3-yne-1-carboxylate*, b. p. (bath temp.) 60°/0·1 mm., $n_D^{21}$ 1·4591, was isolated in small yield from the neutral fraction in another experiment (Found : C, 73·15; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

Yields of the acid were 34, 36, and 11% when the solvents employed were ethyl methyl ketone, acetone and glacial acetic acid, other conditions being unchanged.

*Pent-4-yne-1 : 1-dicarboxylic Acid.*—(*a*) Ethyl malonate (9·6 g.) was added to a solution of sodium ethoxide (from 1·0 g. of sodium) in dried ethanol (20 c.c.) at 25°. Addition of but-3-ynyl toluene-*p*-sulphonate (9·1 g.) resulted in precipitation of sodium toluene-*p*-sulphonate, which was collected after 24 hr. (7·3 g., 95%). An odour of vinylacetylene was noticed. Isolation and distillation of the neutral portion gave a fraction (0·45 g.), b. p. 69—129°/0·1 mm., which was hydrolysed with potassium hydroxide at room temperature. Crystallisation of the solid acid fraction from benzene gave the *acid* (250 mg., 3·5%), m. p. 101·5—102° after recrystallisation (Found : C, 53·75; H, 4·9. $C_7H_8O_4$ requires C, 53·85; H, 5·15%).

(*b*) 4-Iodobut-1-yne (6 g.) was added to a suspension of ethyl sodiomalonate [from sodium (0·7 g.) and diethyl malonate (5·3 g.)] in ethanol (15 c.c.), and the mixture stirred at 20° for 48 hr. The alkaline suspension was diluted with water and the neutral product isolated. Distillation gave unchanged diethyl malonate and a fraction from which substantially pure *diethyl pent-4-yne-1 : 1-dicarboxylate* (0·5 g.), b. p. 118°/14 mm., $n_D^{15}$ 1·4428, was obtained (Found : C, 61·75; H, 7·85. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·55%). The ester gave a white silver salt. Hydrolysis of the ester (270 mg.) afforded crude pent-4-yne-1 : 1-dicarboxylic acid (140 mg.), m. p. (K) 101—102° after recrystallisation from benzene. No depression of melting-point was observed on admixture with a sample prepared as under (*a*).

*5-Cyanopent-1-yne.*—Pent-4-ynyl toluene-*p*-sulphonate (24 g.), potassium cyanide (12 g.), and 80% ethanol (100 c.c.) were heated under reflux for 48 hr. Water was added and the mixture was extracted with ether. Evaporation of the dried extract, followed by distillation, gave the *cyanide* (6·9 g., 75%), b. p. 65·5°/7 mm., $n_D^{17}$ 1·4409 (Found : C, 77·2; H, 7·35. $C_6H_7N$ requires C, 77·4; H, 7·6%).

The cyanide was obtained in only 60% yield when the solvent was aqueous acetone : ether extraction of the acidified aqueous layer gave 4-methyl-2 : 4-dihydroxypentane-2-carboxylactone (*ca.* 12 g.), b. p. 68—69°/0·4 mm., which crystallised from benzene in needles, m. p. (K) 66·5—67·5° (Found : C, 58·3; H, 8·3. Calc. for $C_7H_{12}O_3$ : C, 58·3; H, 8·4%). Light absorption : $\lambda_{max.}$ 2210 Å, $\varepsilon = 72$. (Henze, Thompson, and Speer, *J. Org. Chem.*, 1943, **8**, 17, give m. p. 65°.)

*Pent-4-yne-1-carboxylic Acid.*—(*a*) 5-Cyanopent-1-yne (20 g.) was heated under reflux with 10% potassium hydroxide solution (200 c.c.) for 7 hr., and the solution then acidified and extracted with ether. Evaporation of the dried extract followed by distillation gave the *acid* (I, $n = 3$) (21·9 g., 90%), m. p. *ca.* −8°, b. p. 106°/9 mm., $n_D^{17}$ 1·4500 (Found : C, 63·9; H, 7·3. $C_6H_8O_2$ requires C, 64·25; H, 7·15%). The p-*bromophenacyl* ester crystallised in iridescent plates, m. p. (K) 74·5°, from ethanol (Found : C, 54·25; H, 4·35. $C_{14}H_{13}O_3Br$ requires C, 54·35; H, 4·25%). Hydrogenation of the acid in ethyl acetate with platinic oxide catalyst (uptake : 101% of theory) gave hexanoic acid, identified as its *p*-bromophenacyl ester, m. p. (K) 71° undepressed on admixture with an authentic specimen, m. p. (K) 70·5—71°.

(*b*) Chromic acid (6N ; 10 c.c.) was slowly added to a stirred and cooled (*ca.* 10°) solution of hex-5-yn-1-ol (1·4 g.) in acetone (10 c.c.). After 30 min. the acid fraction was isolated with ether ; distillation gave the acid (410 mg., 27%), b. p. 135°(bath temp.)/14 mm., $n_D^{19}$ 1·4502. The *p*-bromophenacyl ester was identical with that derived from 5-cyanopent-1-yne.

The neutral fraction was heterogeneous but, after purification *via* the silver derivative, it

gave an ester (200 mg.), b. p. 120°(bath temp.)/0·3 mm., $n_D^{20}$ 1·4631, which was evidently *hex-5-ynyl pent-4-yne-1-carboxylate* (Found: C, 74·35; H, 8·1. $C_{12}H_{16}O_2$ requires C, 74·9; H, 8·4%).

*Diethyl Hex-5-yne-1 : 1-dicarboxylate.*—(*a*) Diethyl malonate (70·5 g.) was slowly added to a hot, stirred solution of sodium ethoxide [from sodium (10 g.)] in dry ethanol (200 c.c.), and the solution was heated under reflux for 30 min. Pent-4-ynyl toluene-*p*-sulphonate (100 g.) was added during 1 hr., and after a further 4 hr., the cooled, neutral mixture was filtered, most of the ethanol removed, the filtrate and precipitate added to water (1 litre), and the neutral fraction isolated with ether and carefully distilled to give six fractions.

It was evident from the ethynyl determinations that the lower fractions contained some diethyl 2-methylene*cyclo*pentane-1 : 1-dicarboxylate (see below), and the higher fractions a little of the disubstituted ester. Redistillation of fraction 3 (b. p. 95—97°/0·2 mm.; $n_D^{17}$ 1·4458) obtained in another experiment gave essentially pure *diethyl hex-5-yne-1 : 1-dicarboxylate* (Found: C, 63·95; H, 7·95; •C:CH, 10·95. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0; •C:CH, 11·1%). When fraction 6 (b. p. 103—140°; $n_D^{17}$ 1·4635) was redistilled the main portion had b. p. 130—134°/0·2 mm., and solidified on being set aside at 20°. The solid was freed from adhering liquid which contained unchanged toluene-*p*-sulphonate, and was recrystallised at −6° from light petroleum (b. p. 30—40°) giving *diethyl undeca-1 : 10-diyne-6 : 6-dicarboxylate* as prisms, m. p. 31—32° (open tube). Analyses were erratic, although an ethynyl determination showed the material to be pure (Found: •C:CH, 17·3. $C_{17}H_{24}O_4$ requires •C:CH, 17·3%).

(*b*) From a similar condensation between ethyl sodiomalonate [from sodium (5 g.) and ethyl malonate (35 g.)] in dry ethanol (100 c.c.) and 5-iodopent-1-yne (32 g.), the following were obtained on distillation of the neutral fraction: ethyl malonate (5 g.); a fraction (i) (20·6 g.), b. p. 83—108°/0·6 mm., $n_D^{22}$ 1·4532; and a fraction (ii) (3 g.), b. p. 134°/0·6 mm., $n_D^{22}$ 1·4600. Fraction (i) was mainly 2-*methylene*cyclo*pentane-1 : 1-dicarboxylate*, b. p. 67—69°/0·1 mm., $n_D^{19}$ 1·4553 (Found: C, 63·8; H, 8·05. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%). An ethynyl determination indicated the presence of *ca.* 10% of the isomeric acetylenic ester, which was later confirmed by an infra-red examination.

Catalytic hydrogenation required 98% of the calculated volume of hydrogen. The saturated ester was hydrolysed with aqueous potassium hydroxide to give 2-methyl*cyclo*pentane-1 : 1-dicarboxylic acid, which separated in needles, m. p. (K) 171—172°, from ether (Colman and Perkin, *J.*, 1888, 193, give m. p. 173—175°). Decarboxylation by distillation gave 2-methyl-*cyclo*pentane-1-carboxylic acid, b. p. (bath temp.) 120°/14 mm., $n_D^{19.5}$ 1·4520, identified as the amide, which after sublimation (80°/0·1 mm.) followed by crystallisation from benzene had m. p. (K) 151—153° (Ney, Crouch, Rannefeld, and Lochte, *J. Amer. Chem. Soc.*, 1943, **65**, 770, describe the acid as having b. p. 220°, $n_D^{20}$ 1·4521, and as forming an amide, m. p. 149—150°).

*Hex-5-yne-1 : 1-dicarboxylic Acid.*—Diethyl hex-5-yne-1 : 1-dicarboxylate (4·5 g.) was shaken for 5 min. with a solution of potassium hydroxide (4·4 g.) in water (5 c.c.), and the resultant solution was set aside for 16 hr. at 18°. Several crystallisations of the solid acid fraction (2·8 g., 85%) from benzene gave the *acid* as needles, m. p. (K) 94—95° (decomp.) (Found: C, 56·5; H, 5·9. $C_8H_{10}O_4$ requires C, 56·45; H, 5·9%).

*Hex-5-yne-1-carboxylic Acid* (I; $n = 3$).—(*a*) Diethyl hex-5-yne-1 : 1-dicarboxylate (33·5 g.; fraction 3 from the experiment described above) was dissolved in a 5% aqueous ethanolic solution of potassium hydroxide (350 c.c.) and the mixture set aside at 20° for 3 days. After most of the ethanol had been removed by distillation, the solution was acidified and heated under reflux for 1 hr. On cooling, 2-methyl*cyclo*pent-1-ene-1-carboxylic acid (0·16 g.) separated in needles, which had m. p. (K) 132·5—133° after recrystallisation from nitromethane. The filtrate was thoroughly extracted with ether and the dried extract was evaporated and distilled. Hex-5-yne-1-carboxylic acid (15·6 g., 80%), b. p. 89—92°/0·05 mm., $n_D^{21}$ 1·4520, formed a mass of needles, m. p. 20°, raised to 22—22·5°, after recrystallisation from light petroleum (b. p. 40—60°). (Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4263, describe the acid as an oil, b. p. 93—94°/0·1 mm., $n_D^{25}$ 1·4495.) The p-*bromophenacyl* ester crystallised from aqueous ethanol in needles, m. p. (K) 71·5—72·5° (Found: C, 55·85; H, 4·5. $C_{15}H_{15}O_3Br$ requires C, 55·75; H, 4·7%). The acid absorbed 98% of the calculated volume of hydrogen to give hexane-1-carboxylic acid [*p*-bromophenacyl ester, m. p. 71° (Huntress and Mulliken, "Identification of Pure Organic Compounds," Wiley, London, 1941, give m. p. 72°)].

When other fractions of less pure diethyl hex-5-yne-1 : 1-dicarboxylate were hydrolysed, the yields of hex-5-yne-1-carboxylic acid were in approximate agreement with those to be expected from their estimated ethynyl group content. The overall yield of hex-5-yne-1-carboxylic acid from the toluene-*p*-sulphonate was 44%.

(*b*) Hex-5-yne-1 : 1-dicarboxylic acid (1·1 g.) was slowly heated to 160° under reduced pressure (18 mm.), simultaneous decarboxylation and distillation then occurring. The acid (750 mg., 92%) had b. p. 110° (bath temp.)/0·06 mm., $n_D^{21}$ 1·4540.

*Ethyl Hex-5-yne-1-carboxylate.*—A solution of hex-5-yne-1-carboxylic acid (8·0 g.) in absolute ethanol (50 c.c.) containing sulphuric acid (1·5 c.c.) was set aside at 20° for 5 days. Isolation with ether followed by distillation gave the *ester* (8·1 g., 84%), b. p. 96—97°/20 mm., $n_D^{23}$ 1·4355 (Found: C, 69·85; H, 9·2; ·C:CH, 16·2. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15; ·C:CH, 16·2%).

2-*Methylene*cyclo*pentane*-1 : 1-*dicarboxylic Acid.*—Diethyl 2-methylene*cyclo*pentane-1 : 1-dicarboxylate (5·5 g.; containing *ca.* 10% of the isomeric acetylenic ester) was shaken with a solution of potassium hydroxide (7·5 g.) in water (8 c.c.) for 2 hr. and the resultant solution was set aside for 4 days. The acid fraction was then isolated by continuous extraction with ether and the dried extract was evaporated to leave a solid residue. Trituration of the crystalline mass with benzene–light petroleum gave the *acid* (3·3 g., 80%) as needles, m. p. 120—130° (decomp.), unaltered after several crystallisations from nitromethane (Found: C, 56·3; H, 5·85. $C_8H_{10}O_4$ requires C, 56·45; H, 5·9%). Light absorption: rising absorption down to 2150 Å, $\varepsilon = 945$ and 322 at 2150 Å and 2300 Å, respectively.

2-*Methyl*cyclo*pent*-1-*ene*-1-*carboxylic Acid.*—(*a*) 2-Methylene*cyclo*pentane-1 : 1-dicarboxylic acid (3 g.) was distilled at 0·1 mm., giving the monocarboxylic acid (2·2 g., 98%), which formed needles, m. p. (K) 131—132° after crystallisation from nitromethane (Found: C, 66·35; H, 7·85. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 8·0%). Light absorption: $\lambda_{max.}$ 2300 Å, $\varepsilon = 10{,}500$. Shimizu (*loc. cit.*) gives m. p. 132°.

The structure of the acid was confirmed by catalytic hydrogenation (absorption 97% of theoretical value) to 2-methyl*cyclo*pentane-1-carboxylic acid, $n_D^{20}$ 1·4510 [amide, m. p. (K) 152—154° undepressed on admixture with the amide, m. p. (K) 151—153°, originating from diethyl 2-methyl*cyclo*pentane-1 : 1-dicarboxylate].

(*b*) Diethyl 2-methylene*cyclo*pentane-1 : 1-dicarboxylate (3 g.) was shaken for 4 hr. with a solution of potassium hydroxide (3·5 g.) in water (6 c.c.), the hydrolysis being completed under reflux for a further 3 hr. After being washed with ether, the cooled solution was neutralised and evaporated to dryness. Dilute sulphuric acid (1 : 1; 7 c.c.) was added, the solution was brought to boiling, and the monocarboxylic acid was removed by steam-distillation. The acid (1·24 g., 74%) formed prismatic needles, m. p. (K) 131—132°.

*Methyl* 2-*Methyl*cyclo*pent*-1-*ene*-1-*carboxylate.*—2-Methyl*cyclo*pent-1-ene-1-carboxylic acid (169 mg.) was esterified with diazomethane; distillation furnished the *ester* (174 mg., 93%), b. p. 85—90°(bath temp.)/18 mm., $n_D^{19}$ 1·4750 (Found: C, 68·4; H, 9·05. $C_8H_{12}O_2$ requires C, 67·8; H, 8·6%; other samples underwent explosive decomposition). Light absorption: $\lambda_{max.}$ 2315 Å, $\varepsilon = 10{,}300$.

*Ethyl* 2-*Methyl*cyclo*pent*-1-*ene*-1-*carboxylate.*—A solution of 2-methyl*cyclo*pent-1-ene-1-carboxylic acid (600 mg.) in dry ethanol (5 c.c.) containing sulphuric acid (0·1 c.c.) was heated under reflux for 10 hr. Isolation and distillation of the neutral fraction gave the *ester* (400 mg., 50%), b. p. 190°(bath temp.)/520 mm., $n_D^{21}$ 1·4660 (Found: C, 69·7; H, 9·05. $C_9H_{14}O_2$ requires C, 70·0; H, 9·1%). Light absorption: $\lambda_{max.}$ 2325 Å, $\varepsilon = 10{,}300$.

Much of the acid was recovered unchanged from an attempted esterification at 20° (36 hr.). The ester was also remarkably resistant to hydrolysis: a small portion had undergone little hydrolysis after contact with aqueous potassium hydroxide (30%) for several days.

*Diethyl Hept-6-yne*-1 : 1-*dicarboxylate.*—Hex-5-ynyl toluene-*p*-sulphonate (3 g.; prepared from crude hex-5-yn-1-ol containing some tetrahydro-2-pyranylmethanol) in dry ether (10 c.c) was added to a stirred suspension of ethyl sodiomalonate [from sodium (0·3 g.) and ethyl malonate (2·1 g.)] in dry ethanol (10 c.c.), the suspension heated under reflux for 15 hr., and the neutral fraction was then isolated with ether. Distillation gave unchanged ethyl malonate and two fractions: (*a*) 1·27 g., b. p. 120—125°(bath temp.)/0·01 mm., $n_D^{18}$ 1·4470; and (*b*) 0·75 g., b. p. 190°(bath temp.)/0·01 mm., which partly solidified on cooling. Fraction (*a*) was redistilled to give substantially pure *diethyl hept-6-yne*-1 : 1-*dicarboxylate* (1·1 g., 40%), b. p. 110°(bath temp.)/0·005 mm., $n_D^{22}$ 1·4455 (Found: C, 64·5; H, 8·3; ·C:CH, 10·8. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3; ·C:CH, 10·4%). Newman and Wotiz (*J. Amer. Chem. Soc.*, 1949, **71**, 1293) did not isolate this ester although it was an intermediate in their route to hept-6-yne-1-carboxylic acid. The crystalline material from fraction (*b*), after crystallisation from light petroleum, had m. p. (K) 71—72°, undepressed on admixture with a specimen of tetrahydro-2-pyranylmethyl toluene-*p*-sulphonate, m. p. (K) 72·5° (cf. Eglinton, Jones, and Whiting, *loc. cit.*).

*Hept-6-yne*-1-*carboxylic Acid.*—Diethyl hept-6-yne-1 : 1-dicarboxylate (310 mg.) was shaken with potassium hydroxide solution (0·7 c.c.; *ca.* 50%) and the solution was set aside for 18 hr.

Isolation of the acid fraction with ether gave hept-6-yne-1 : 1-dicarboxylic acid (230 mg.), m. p. 80—86°. A small sample crystallised from benzene–light petroleum (b. p. 60—80°) in rhombs, m. p. (K) 84—85°. The acid was heated at 160° for 1 hr., yielding hept-6-yne-1-carboxylic acid (130 mg., 72%), m. p. 18—20° [Newman and Wotiz (*loc. cit.*) give m. p. 20°]. The acid was characterised by conversion, *via* the acid chloride, into the amide which separated from light petroleum (b. p. 60—80°) in needles, m. p. (K) 89·5—90° undepressed on admixture with a genuine sample, m. p. (K) 90·5—91°, kindly supplied by Professor M. S. Newman.

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## 608. *Temperature Coefficients of Fluorescence.*

By E. J. BOWEN and R. J. COOK.

Measurements have been made of the changes of fluorescence intensity with temperature of a series of substituted anthracenes in four organic solvents. The temperature coefficients are in some instances positive and in others negative, and the effects are explained on the basis of intermolecular attractions between solvent molecules and the electronically excited solute molecules.

THE fluorescence intensities of six anthracene derivatives, prepared by synthesis and purified by chromatography, have been measured in dilute solution in four organic solvents at temperatures between 15° and 60°. The liquids were contained in a water-jacketed tube for temperature control and illuminated by a narrow beam of 3650 Å radiation. The fluorescence was measured at right angles to the exciting beam by a balanced photomultiplier device as described by Bowen and Metcalf (*Proc. Roy. Soc.*, 1951, *A*, **206**, 437). The concentration of the solute was about $10^{-4}$M and fixed at the point where the measurable fluorescence was a maximum owing to the balance between the geometry of the apparatus and the fraction of light absorbed (Bowen and Coates, *J.*, 1947, 105).

The solutions were deoxygenated by passage of a fine stream of coal gas purified by charcoal and silica gel, and the small amount of residual oxygen quenching allowed for from a knowledge of the oxygen content of the gas (0·7% by vol.) and the effect of dissolved air on the fluorescence. The solvents used were "AnalaR" benzene and acetone, B.P. chloroform, and aromatic-free kerosene purified by treatment with fuming sulphuric acid and passage through a column of activated alumina. Within the limits of error fluorescence was found to change linearly with temperature over the small range investigated. The measured intensities were converted into absolute fluorescence efficiencies by comparison with the value 0·24 for anthracene in benzene (Bowen and Williams, *Trans. Faraday Soc.*, 1939, **35**, 765), since all the solutions absorbed the same fraction of the incident light and the wave-length variation of the photomultiplier sensitivity was negligible. The results are given in Table 1.

TABLE 1. *Fluorescence efficiencies* F *of very dilute solutions of anthracenes, where* $F_0$ = *efficiency at* 0° and $F = F_0(1 - 10^{-4}\alpha t)$ *up to* $t = 60°$.

| Anthracene | | Kerosene | $CHCl_3$ | $C_6H_6$ | $COMe_2$ | Anthracene | | Kerosene | $CHCl_3$ | $C_6H_6$ | $COMe_2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Unsubst. | $F_0$ | 0·267 | 0·090 | 0·234 | 0·263 | 1-Cl | $F_0$ | 0·081 | 0·048 | 0·079 | 0·094 |
| | $\alpha$ | 6·9 | −3·9 | −3·1 | 2·45 | | $\alpha$ | 2·18 | −0·82 | −0·44 | 1·67 |
| 9-Ph | $F_0$ | 0·687 | 0·458 | 0·773 | 0·649 | 1 : 5-$Cl_2$ | $F_0$ | 0·064 | 0·041 | 0·073 | 0·075 |
| | $\alpha$ | 34·9 | 23·6 | 29·4 | 19·3 | | $\alpha$ | 1·76 | 0·29 | 1·31 | 1·91 |
| 9 : 10-$Ph_2$ | $F_0$ | 0·758 | 0·65 | 0·80 | 0·776 | 9 : 10-$Cl_2$ | $F_0$ | 0·746 | 0·590 | 0·815 | 0·741 |
| | $\alpha$ | 7·34 | 0 | 0 | −9·55 | | $\alpha$ | 58 | 36 | 46 | 56 |

The following facts are apparent. All the efficiencies fall with rising temperature for the substances in kerosene solutions, and fall more steeply than in the other solvents.

Not only are the temperature variations less in benzene, chloroform, and acetone, but in the first two solvents the solutes anthracene and 1-chloroanthracene show an inverse temperature effect, and 9 : 10-diphenylanthracene does so in the last.

In mixed kerosene–bromobenzene solutions of anthracenes the fluorescence is partly quenched by the bromobenzene and the temperature variations sometimes change sign, as shown in Table 2.

TABLE 2. *Fluorescence efficiencies* F *of very dilute solutions of anthracenes in kerosene containing* B *vol.* % *of bromobenzene, where* $F_0$ = *efficiency at* 0° *and* $F = F_0(1 - 10^{-4}\alpha t)$ *up to* $t = 60°$.

| | | B, % | | | | | | B, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anthracene | | 0 | 10 | 20 | 40 | Anthracene | | 0 | 10 | 20 | 40 |
| Unsubst.* | $F_0$ | 0·267 | 0·092 | 0·054 | 0·028 | 1-Cl | $F_0$ | 0·081 | 0·040 | 0·039 | 0·026 |
| | $\alpha$ | 6·9 | 0 | −0·71 | −0·89 | | $\alpha$ | 2·18 | 0·56 | 0 | −0·51 |
| 9-Ph | $F_0$ | 0·687 | 0·496 | 0·435 | 0·394 | 1 : 5-$Cl_2$ | $F_0$ | 0·064 | 0·049 | 0·038 | 0·028 |
| | $\alpha$ | 34·9 | 31·3 | 29·8 | 29·3 | | $\alpha$ | 1·76 | 0·84 | 0·20 | −0·16 |
| 9 : 10-$Ph_2$ | $F_0$ | 0·758 | 0·676 | 0·641 | 0·579 | 9 : 10-$Cl_2$ | $F_0$ | 0·746 | 0·745 | 0·749 | 0·746 |
| | $\alpha$ | 7·34 | 7·78 | 9·78 | 9·34 | | $\alpha$ | 58 | 55 | 54 | 52 |

* For $B = 3\%$, $F_0 = 0{\cdot}165$ and $\alpha = 2$.

Increase of fluorescence intensity with increase of temperature, sometimes referred to as a negative temperature coefficient of quenching, has been explained in terms of molecular interactions of molecules in the ground state (Bowen and Coates, *J.*, 1947, 105). Though this undoubtedly occurs in some systems, in these instances interaction between excited solute and normal solvent molecules seems more likely.

FIG. 1.

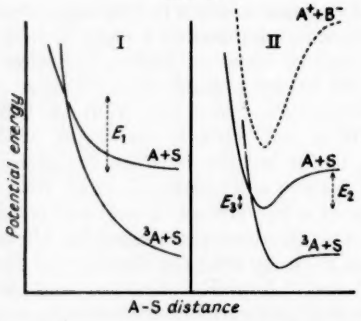


FIG. 2.

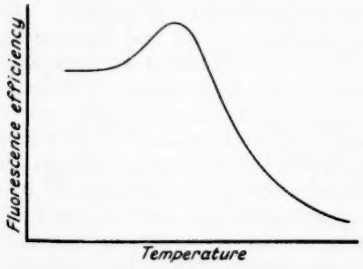


Fig. 1, I, shows repulsional interaction curves between solvent molecules S and fluorescent solute molecules A, the curve for the excited molecule A* crossing one for a lower state, probably the triplet level $^3$A, in which energy available for fluorescence is degraded. Quenching then depends on the molecules A* + S having sufficient energy $E_1$ to rise to the crossing point, and on the efficiency of change over to the other curve at that point.

According to a recent theory by Mulliken (*J. Amer. Chem. Soc.*, 1952, **74**, 811), the proximity of an $A^+B^-$ interaction curve, as shown broken in Fig. 1, II, causes the A,S interaction curves to develop minima corresponding to the ionic attraction. We may then write the following scheme :

| | Rate constant |
|---|---|
| 1. $A + h\nu \longrightarrow A^*$ | 1 |
| 2. $A^* \longrightarrow A + h\nu'$ | $k_f$ |
| 3. $A^* + S \longrightarrow {}^3A + S$ | $k_d e^{-E_1/RT}$ |
| 4. $A^* + S \longrightarrow AS^*$ | $k_1$ |
| 5. $AS^* \longrightarrow A^* + S$ | $k_2 e^{-E_2/RT}$ |
| 6. $AS^* \longrightarrow {}^3A + S$ | $k_3 e^{-E_3/RT}$ |

whence, if $F$ = fluorescence efficiency,

$$1/F = 1 + k_d/k_f e^{-E_1/RT} + k_1 k_3/k_f(k_2 e^{(E_3 - E_2)/RT} + k_3)$$

This presupposes that A* is quenched in two different ways, by reaction (3) of unoriented molecules, and by reaction (6) of an oriented molecular complex. The kinetic treatment of such a scheme is hampered by lack of knowledge of collision processes in liquids. It is sometimes assumed that collisional rates between solute and solvent molecules decrease with rising temperature in a manner proportional to the viscosity (Moelwyn-Hughes, " Kinetics of Reactions in Solution," Clarendon Press, 1933, p. 20); on the other hand. encounter rates are inversely proportional to the viscosity divided by the absolute temperature (Umberger and LaMer, *J. Amer. Chem. Soc.*, 1945, **67**, 1099). If reactions (3)—(6) depended directly on the viscosity, their rate constants would include a temperature dependence of $e^{E/RT}$, where $E = 3{\cdot}3$ kcal. for kerosene as an example. That this is unlikely is shown by several considerations. Inverse temperature coefficients of quenching might then be found in solvents of high viscosity change, instead of being associated with solvents of molecular complexing type. It is also relevant that anthracene has practically the same fluorescence efficiency and temperature coefficient of fluorescence in saturated aliphatic paraffin solutions of viscosities varying by a 300 : 1 ratio and of viscosity temperature coefficients varying by a factor of 14 (Metcalf, D.Phil.Thesis, Oxford, 1950). We shall therefore assume for simplicity that the frequency factors of all the reactions are independent of temperature, and that the exponential factors relate to energies of the potential-energy diagram. The scheme then gives an $F$–$T$ curve of the shape shown in Fig. 2 (assuming $E_2 > E_3$).

Experimental data for a single solution covering all the features of such a predicted curve have not yet been obtained, because of the practical difficulties of measurement over a very wide temperature range. The results of Tables 1 and 2, however, may well represent small segments of curves of Fig. 2 type, including the modification without a maximum where $E_2 < E_3$. Further progress in this field needs a better understanding of kinetic interactions of solute and solvent molecules, as well as more extended measurements on suitably chosen systems.

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## 609. *Chemistry of the Vitamin $B_{12}$ Group. Part II.* Synthesis of 5 : 6-Dimethyl-1-α-D-ribofuranosylbenziminazole.*

By A. W. JOHNSON, G. W. MILLER, J. A. MILLS, and A. R. TODD.

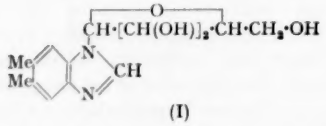
Various synthetic routes to glycosylbenziminazoles have been examined and condensation of the free bases with *O*-acetylglycosyl halides has been shown to yield a mixture of the α- and β-anomers of the *N*-glycosyl compounds. 5 : 6-Dimethyl-1-α-D-ribofuranosylbenziminazole, a degradation product of vitamin $B_{12}$, has been synthesised by this method.

DEGRADATION of vitamin $B_{12}$ with mineral acid yields, among other products, 5 : 6-dimethylbenziminazole (Brink and Folkers, *J. Amer. Chem. Soc.*, 1949, **71**, 2951; 1950, **72**, 4442; Beavan, Holiday, Johnson, Ellis, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1949, **1**, 957), its 1-α-D-ribofuranosyl derivative (I) (Brink *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 1866; 1952, **74**, 2856) and the 2′(or 3′)-phosphate of (I) (Buchanan, Johnson, Mills, and Todd, *J.*, 1950, 2845). A synthesis of (I) has been described by the Merck group of workers (Holly *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 1866; 1952, **74**, 4521); 4 : 5-dimethyl-2-nitro-*N*-(5′-*O*-trityl-D-ribofuranosyl)aniline (II) was hydrogenated, and then cyclised with *iso*propyl formimidate hydrochloride and the triphenylmethyl group was finally removed by hydrolysis, yielding (I).

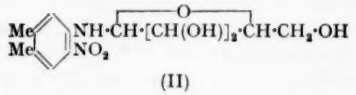
The anomeric compound, 5 : 6-dimethyl-1-β-D-ribofuranosylbenziminazole, was synthesised by the same route save that the reduction and cyclisation steps were carried out starting with the diacetyl derivative of (II). It is of some interest that small amounts of the α-ribosyl compound were formed in addition to the β-compound; rather similar

* Part I, *J.*, 1950, 2845.

effects of acetylation of intermediates on the course of the cyclisation step in purine nucleoside syntheses have been reported from this laboratory (Kenner, Todd, *et al.*, *J.*, **1946**, 852; **1948**, 2265; **1949**, **1613**) and have been ascribed to chelation. The configuration at the glycoside carbon in these ribosylbenziminazoles was assigned on the basis of periodate oxidation studies and the optical rotations of the glycosyl derivatives and their



(I)



(II)

picrates. The α-configuration of the ribosylbenziminazole obtained from vitamin $B_{12}$ is surprising, in view of the uniform β-configuration of all the natural purine and pyrimidine ribonucleosides.

Our own work in this field, which was completed before the appeareance of any experimental details of the American syntheses, led to an independent synthesis of (I), and in view of the difficulties encountered in all efforts to synthesise glycofuranosylbenziminazoles it seems desirable to place our results on record. The formal resemblance of (I) to the purine nucleosides naturally suggested the application of synthetic methods which had been successful in that series (for review see Kenner, *Fortsch. Chemie Org. Naturstoffe*, **1951**, **8**, 96). These were of two main types: (1) the conversion of a mono-*N*-glycosyl-*o*-phenylenediamine into a benziminazole by a process introducing one more carbon atom, and (2) the reaction of a preformed benziminazole with an *O*-acetylglycosyl halide. The synthesis of glycopyranosyl compounds by methods of type (1) is relatively straightforward (Part I, *loc. cit.*; Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, **1950**, **2**, 491, 503, 512, 579; Holly *et al.*, *loc. cit.*) but is much less satisfactory for glycofuranosyl compounds. The synthesis of (I) by Holly *et al.* (*loc. cit.*) is indeed of this type, but the overall yields reported by them were both low and variable. Our experience was similar and as we were unable to effect any material improvements we abandoned this route.

Methods of type (2), employing a performed benziminazole, have the advantage of directness and are attractive in the case of 5 : 6-dimethylbenziminazole, whose symmetrical structure removes the chief drawback to such methods, *viz.*, ambiguity as regards position of the entering sugar residue. In Part I (*loc. cit.*) we described a synthesis of 1-β-D-glucopyranosyl-5 : 6-dimethylbenziminazole from the silver salt of 5 : 6-dimethylbenziminazole and acetobromoglucose, but the yield was very poor. Other workers (Mamalis, Petrow, and Sturgeon, *loc. cit.*; Weygand, Wacker, and Wirth, *Z. Naturforsch.*, **1951**, **66**, 25; Weygand and Wirth, *Chem. Ber.*, **1952**, **85**, 1000) have made a number of glycosylbenziminazoles in the same way, but only in reactions using silver 5 : 6-dichlorobenziminazole (Weygand, Wacker, and Wirth, *loc. cit.*) were really satisfactory yields obtained. The poor results are probably attributable largely to the heterogeneous nature of the initial reactions. Our attempts to improve matters by using a mixture of the benziminazole with silver oxide, or by substituting zinc, cadmium, or thallium derivatives were unsuccessful. In the course of these studies we confirmed Davoll and Lowy's observation (*J. Amer. Chem. Soc.*, **1951**, **73**, 5781) that chloromercuri-derivatives of benziminazole are more satisfactory than silver derivatives in such condensations, although considerable darkening usually occurred under the conditions recommended by them (boiling xylene); both Davoll and Lowy (*loc. cit.*) and Weygand and Wirth (*loc. cit.*) prepared the β-anomer of (I) by this method. In all condensations of metal derivatives of benziminazoles with tetra-*O*-acetylglucosyl bromide the occurrence of a Walden inversion has been assumed (cf. Howard, *J.*, **1950**, **1045**) and the products have accordingly been formulated as 1-tetra-*O*-acetyl-β-D-glucosylbenziminazoles.

In a further attempt to improve this type of synthesis of *N*-glucosylbenziminazoles the reaction between acetohalogeno-sugars and metal-free benziminazoles was investigated. This reaction is analogous to that normally employed for the synthesis of pyrimidine nucleosides (cf. Howard, Lythgoe, and Todd, *J.*, **1947**, **1052**; Kenner, *loc. cit.*, p. 108),

starting with acetohalogeno-sugars and 2 : 4-diethoxypyrimidine and proceeding by elimination of ethyl halide from the quaternary salt initially formed. In the case of benziminazoles hydrogen bromide is, of course, liberated, but this can be removed as a salt by working with excess of the base. The reaction between tetra-*O*-acetylglucosyl bromide and benziminazole was carried out in dioxan solution, and the crude 1-D-tetra-*O*-acetylglucosylbenziminazole was deacetylated with mineral acid. Excess of benziminazole was removed by chromatography on alumina, and the glycosyl material subjected to chromatography on charcoal–Hyflo supercel with ethanol as eluant.

By this means 1-β-D-glucopyranosylbenziminazole was obtained, identical with that previously described (Buchanan *et al.*, Mamalis *et al.*, and Davoll and Lowy, *locc. cit.*), as well as an isomeric glucosyl compound which from its optical rotation was identified as the corresponding 1-α-D-glucopyranosylbenziminazole and was produced in about 1/5 of the amount of the β-isomer. The α- and the β-isomer were also separated by fractional crystallisation of the picrates. Although there have been several reports of the preparation of glycosides from *cis*-acetohalogeno-sugars without inversion (or possibly with a double inversion) at the 1-carbon atom of the sugar (Howard, *loc. cit.*) there have been but few reports of this phenomenon in the *N*-glycosyl series; Davoll and Lythgoe (*J.*, 1949, 2526), however, isolated both isomers of 3′ : 4′-diacetyl-2′-deoxy-D-ribopyranosyltheophylline by reaction of the silver salt of the base with an acetohalogenoribose. Reaction of 5 : 6-dimethylbenziminazole with acetobromoglucose yielded similarly both forms of the *N*-D-glucopyranosyl derivative, and the α-form, not previously described, was further characterised as its picrate.

For the preparation of the *N*-D-ribofuranosyl compounds, tri-*O*-acetyl-D-ribofuranosyl chloride was first prepared. The tetra-*O*-acetyl-D-ribofuranose required was obtained from 1 : 2 : 3-tri-*O*-acetyl-5-tritylribose (Howard, Lythgoe, and Todd, *J.*, 1947, 1052; Bredereck and Hoepfner, *Ber.*, 1948, **81**, 51) or by direct acetylation of D-ribose. The latter process, studied by Zinner (*Ber.*, 1950, **83**, 153), has now been made less capricious by use of dioxan as solvent and a small quantity of pyridine as catalyst, although the yields obtained were then lower.

Condensation of tri-*O*-acetyl-D-ribofuranosyl chloride with 5 : 6-dimethylbenziminazole was carried out as in the glucose series, and the crude ribosyl mixture was chromatographed as before. The two isomers were separated, the β- (10%) being more abundant than the required α-isomer (2%). The latter was identical with the nucleoside derived from vitamin $B_{12}$ (Brink and Folkers, *J. Amer. Chem. Soc.*, 1952, **74**, 2856). When tri-*O*-acetylribofuranosyl bromide was used (cf. Howard, Lythgoe, and Todd, *loc. cit.*), its additional reactivity was counteracted by its instability and the yield of the α-ribosyl compound was not improved. The use of acetonitrile as solvent likewise offered no advantage.

Being a rather weak base ($pK_a$ 5·53), benziminazole may not be very effective in promoting base-catalysed side reactions such as the elimination of hydrogen halide from *O*-acylglycosyl halides to produce glycoseens (cf. Maurer, *Ber.*, 1929, **62**, 232) or 1 : 6-anhydro-sugars (cf. Micheel, *ibid.*, p. 687). Nevertheless, reactions other than the formation of *N*-glycosyl compounds always occurred, and little or no unchanged tetra-*O*-acetylglycosyl halide was normally present at the end of the reaction. In one experiment, tri-*O*-acetyl-1 : 6-anhydroglucose was provisionally identified on a paper chromatogram of the non-basic components of the reaction mixture.

The reaction of the free benziminazole bases and *O*-acylglycosyl halides compares favourably with the reactions involving the heavy metal derivatives of the benziminazoles, especially in ease of manipulation, and the yields obtained are of the same order as those reported from the condensations using the mercury derivatives (Davoll and Lowy, *loc. cit.*).

## Experimental

Rotations refer to pyridine solutions, unless otherwise stated.

1-D-*Glucopyranosylbenziminazoles.*—Benziminazole (20 g., 2·2 mols.) and tetra-*O*-acetylglucosyl bromide (32 g., 1 mol.) were dissolved in dioxan (80 c.c.) at 100° and kept at this temperature for 3½ hr., during which crystalline benziminazole hydrobromide separated. Xylene

(300 c.c.) was added to the solution which then was cooled (ice), and solids were removed by filtration. The acetyl groups were removed from the product by heating the xylene solution at 100° with successive quantities of N-hydrochloric acid (3 × 30 c.c.) for 30 min. each and the combined aqueous layers were then made alkaline with aqueous ammonia (*d* 0·88) and evaporated to dryness under reduced pressure. The dark residue was extracted with boiling ethanol (3 × 150 c.c.), and the combined ethanolic extracts were dried by azeotropic distillation with benzene (50 c.c.). The dried solution was brought on to a column of alumina (8 × 2½") and washed exhaustively with ethanol to remove unchanged benziminazole. The progress of the separation was followed by examining the acidified eluate in ultra-violet light, benziminazole being fluorescent. Elution with water rapidly removed the glucosyl derivative from the column and when this eluate was concentrated under reduced pressure to 50 c.c. and cooled at 0° overnight crystalline 1-β-D-glucopyranosylbenziminazole, m. p. 140—141°, separated. Recrystallisation from water gave the pure monohydrate (4·9 g., 21% based on tetra-*O*-acetylglucosyl bromide), m. p. 141—142°, $[\alpha]_D^{15}$ −28° (*c* 2) (Found: Loss at 125° in a high vacuum, 5·6. Calc. for $C_{13}H_{16}O_5N_2,H_2O$: 6·0%). When boiled with dry *iso*propanol (20 c.c. per g.) the hydrate dissolved and the solution quickly deposited the anhydrous product as a fine powder, m. p. 210—212°. This afforded a picrate, m. p. 145—148°, $[\alpha]_D^{15}$ −18° (*c* 2), and a tetra-*O*-acetyl derivative separating from benzene as fine needles, m. p. 152—153°, $[\alpha]_D^{15}$ −27° (*c* 2 in $CHCl_3$). These values are in good agreement with the published data on 1-β-D-glucopyranosylbenziminazole (Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1950, **2**, 593; Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 5781).

The aqueous mother-liquors from the β-D-glucopyranosyl compound were brought on to a column (9 × 2½") of charcoal ("Karbak" grade)–Hyflo supercel (1 : 1; 300 g.), and the column washed with water until the eluate, which contained mainly non-nitrogenous impurities, no longer reduced ammoniacal silver nitrate. The eluant was then changed to ethanol (some batches of charcoal required the addition of 1% of pyridine to the ethanol for elution of the glucoside), and the eluate collected in two main fractions (2 l. each). Each fraction was taken to dryness under reduced pressure and the colourless residue dissolved in a small quantity of water and treated with successive portions of saturated aqueous picric acid. From the first fraction the following picrates were obtained (*c* = 1): $[\alpha]_D^{19}$ +90° (1·55 g.), +80° (0·1 g.), +50° (1 g.), +8° (0·5 g.); and from the second eluate fraction: $[\alpha]_D^{19}$ +47° (2·1 g.) and +23° (0·85 g.). The picrate fractions with $[\alpha]_D^{19} > +80°$ (1·65 g.) were combined and recrystallised from water to give long feathery needles (1·5 g., 3·7% based on tetra-*O*-acetylglucosyl bromide), m. p. 125—135°, $[\alpha]_D^{19}$ +93° (*c* 1·2). The *picrate* appeared to be hydrated but the m. p. range was not decreased after drying (Found: C, 43·0; H, 3·9; N, 13·1; loss at 100° *in vacuo* for 24 hr., 3·5. $C_{19}H_{19}O_{12}N_5,H_2O$ requires C, 43·3; H, 4·0; N, 13·3; $H_2O$, 3·4%). On periodate titration the picrate reacted with 2·02 mols. of oxidant.

The picrate (100 mg.) was decomposed by treating a methanolic solution with small quantities of freshly prepared Dowex 2 ion-exchange resin (1 g.) in the hydroxide form. When the colour of the supernatant liquid had been discharged, the orange resin was separated and the clear solution evaporated to yield 1-α-D-*glucopyranosylbenziminazole* (52 mg.) as a colourless solid which crystallised from ethanol as needles, m. p. 178—179°, $[\alpha]_D^{15}$ +170° (*c* 1·8) (Found, on a sample dried at 105° in a high vacuum: C, 55·6; H, 6·0; N, 10·1. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·8; N, 10·0%). Titration with sodium periodate gave a value of 2·0 mols. of reagent consumed by each mol. of the product.

1-D-*Glucopyranosyl*-5 : 6-*dimethylbenziminazoles*.—5 : 6-Dimethylbenziminazole (10·5 g., 2·2 mols.) and tetra-*O*-acetylglucosyl bromide (13·5 g., 1 mol.) were heated in dry dioxan (32 c.c.) at 100° for 3 hr. The product was then treated as in the previous experiment; xylene (200 c.c.) was added and the filtered solution hydrolysed at 100° with N-hydrochloric acid (3 × 30 c.c.). The combined aqueous layers were made alkaline with aqueous ammonia (*d* 0·88), and the unchanged 5 : 6-dimethylbenziminazole was removed by chromatography on alumina as before. The brown aqueous solution of glucosyl derivatives, contaminated with unchanged glucose, was treated on charcoal ("Karbak")–Hyflo supercel (1 : 1; 300 g.) as before. The alcoholic eluate was collected in 5 fractions (1 l. each). Evaporation of fractions 1—3 gave colourless feathery crystals of 1-β-D-glucopyranosyl-5 : 6-dimethylbenziminazole, which after crystallisation from absolute ethanol had m. p. 248—250° (2·0 g., 20% based on tetra-*O*-acetylglucosyl bromide) undepressed by an authentic specimen (Buchanan, Johnson, Mills and Todd, and Davoll and Brown, *locc. cit.*). It consumed 2·01 mols. of sodium periodate.

Fractions 4 and 5 gave a colourless residue which after crystallisation from water or aqueous alcohol formed needles, m. p. 176°, $[\alpha]_D^{19}$ +171° (*c* 1·2) (0·52 g., 5·1% based on tetra-*O*-

acetylglucosyl bromide) (Found, on a sample dried at 100° over $P_2O_5$ *in vacuo* for 2 days: C, 57·95; H, 6·7; N, 9·4. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%). The corresponding *picrate*, crystallised from aqueous ethanol, had $[\alpha]_D^{19}$ +101° (*c* 1) (Found: C, 45·8; H, 4·4; N, 12·4. $C_{21}H_{23}O_{12}N_5,H_2O$ requires C, 45·4; H, 4·5; N, 12·6%). The m. p. was indefinite and varied with the rate of heating but on very slow heating a value m. p. 205° was obtained, presumably of the anhydrous form. The glycosyl derivative consumed 2 mols. of sodium periodate; the picrate of the oxidised product, after drying *in vacuo* for 2 days at room temperature over $P_2O_5$, had m. p. 185—186°, undepressed in admixture with the picrate of the product obtained from the periodate oxidation of 5:6-dimethyl-1-α-D-ribofuranosylbenziminazole (Brink and Folkers, *J. Amer. Chem. Soc.*, 1952, **74**, 2856, give m. p. 183—185·5°).

*Tetra-O-acetyl-D-ribofuranose.*—D-Ribose (5 g.) was heated with dry dioxan (80 c.c.) and pyridine (0·8 c.c.) on the steam-bath until dissolved. Acetic anhydride (19·2 c.c., 6 mols.) was added dropwise to the stirred hot solution during 1¼ hr. Heating was continued for another 2¼ hr. and the solvent removed at 50° (bath-temp.)/15 mm. The residual yellowish oil was cooled and diluted with ice-water (40 c.c.). A seed crystal of tetra-*O*-acetyl-D-ribofuranose was added and after 2 hr. at 0° the crystalline solid (6·5 g.) was separated, washed, and dried. It then had m. p. 69—75° but after crystallisation from *iso*propanol (100 c.c.) (charcoal) pure tetra-*O*-acetylribofuranose (2 g.), m. p. 81—82°, was obtained. A further quantity (1 g.), m. p. 81—82°, was isolated from the *iso*propanolic mother-liquors after evaporation to half volume under reduced pressure and seeding. Further evaporation and seeding gave a mixture of the furanose and the pyranose form. The yield of tetra-*O*-acetyl-D-ribofuranose obtained decreased when larger batches (*e.g.*, 20 g.) of D-ribose were used. Tri-*O*-acetyl-D-ribofuranosyl chloride was obtained from tetra-*O*-acetyl-D-ribofuranose essentially as described by Zinner (*loc. cit.*).

1-D-*Ribofuranosyl*-5:6-*dimethylbenziminazoles.*—5:6-Dimethylbenziminazole (7·5 g., 2·2 mols.) in dry dioxan (100 c.c.) at 100° was added to the tri-*O*-acetyl-D-ribofuranosyl chloride syrup (1 mol.) prepared from tetra-*O*-acetyl-D-ribofuranose (7·5 g.), and the mixture heated at 100° for 3 hr. The product was treated as in the above preparations of the D-glucopyranosyl compounds; xylene (200 c.c.) was added and the filtered solution repeatedly hydrolysed with N-hydrochloric acid at 100° (3 × 30 c.c.). The combined aqueous layers were made alkaline with aqueous ammonia (*d* 0·88), and the unchanged 5:6-dimethylbenziminazole removed by chromatography on alumina (8 × 2½ cm.). The brown aqueous solution of ribosyl and other carbohydrate derivatives was adsorbed on a column of charcoal ("Karbak")–Hyflo supercel (1:1; 300 g.), and washed exhaustively with water to remove salts and a good deal of the non-nitrogenous material. The ribosides were eluted with ethanol–pyridine (9:1), and the eluate was collected in 7 fractions (1 l. each). Each fraction was diluted with successive portions of water (100 c.c.) and then evaporated to dryness at reduced pressure until all of the pyridine was removed. The residues were each taken up in water (20 c.c.) and then cooled at 0°. Fractions 4—7 yielded colourless solids which were collected, combined and converted into the picrate. After crystallisation from water this had m. p. 175° and it was re-converted into 5:6-dimethyl-1-β-D-ribofuranosylbenziminazole by treatment with Dowex 2 resin in the hydroxide form as described below for the α-isomer. The free base, recrystallised from water, had m. p. 197—200°, $[\alpha]_D^{19}$ −44° (*c* 1) (0·65 g.; 10% based on tetra-*O*-acetylribofuranose), and consumed 1·0 mol. of sodium periodate. These values agree with those given by Holly, Shunk, Peel, and Folkers (*loc. cit.*).

Fractions 1, 2, and 3 from the chromatogram were severally treated with excess of aqueous picric acid. The precipitated picrates were separated, washed, and dried and each had m. p. 210°, $[\alpha]_D^{19}$ +9° (*c* 1). The combined picrates (463 mg.) were crystallised from water, giving 5:6-dimethyl-1-α-D-ribofuranosylbenziminazole picrate (Found: C, 47·3; H, 4·2; N, 14·0. Calc. for $C_{20}H_{21}N_5O_{11}$: C, 47·3; H, 4·2; N, 13·8%).

The picrate consumed 0·92 mol. of sodium periodate; the dialdehyde picrate so formed was crystallised from aqueous ethanol; it had m. p. 185—186°, undepressed on admixture with the picrate of the periodate oxidation product of 1-α-D-glucopyranosyl-5:6-dimethylbenziminazole.

Dowex 2 ion exchange resin in the hydroxide form (1 g.) was added to a warm solution of the picrate of 5:6-dimethyl-1-α-D-ribofuranosylbenziminazole (0·46 g.) in methanol (20 c.c.). The resin was separated and washed with boiling methanol, and the combined methanolic filtrates were taken to dryness. The residual oil (243 mg., 96%) on cooling at 0° or on trituration with ether gave a colourless solid, m. p. 190—195°, which was crystallised first from acetone and then from water, to give the pure α-D-ribofuranosylbenziminazole as colourless needles,

m. p. 198°, $[\alpha]_D^{19}$ +14° (*c* 1) (Found : C, 60·4; H, 6·8; N, 10·0. Calc. for $C_{14}H_{18}O_4N_2$ : C, 60·4; H, 6·5; N, 10·1%). The *iso*propylidene derivative of the glycoside was also used for the purification (Holly *et al.*, *loc. cit.*).

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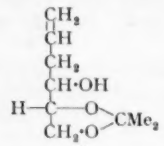
## 610. *A Synthesis of* 2-*Deoxy*-D-*ribose.*

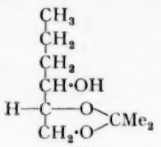
By L. HOUGH.

Allylmagnesium bromide and 2 : 3-*O*-*iso*propylidene-D-glyceraldehyde give 1 : 2-*iso*propylidenedioxyhex-5-en-3-ol, apparently containing largely the *erythro*-isomer. Hydroxylation of this, followed by periodate oxidation and hydrolysis, gave 2-deoxy-D-ribose, isolated *via* the aniline derivative in poor overall yield (cf. *Chem. and Ind.*, 1951, 406).

FISCHER (*Ber.*, 1914, **47**, 186) described the first synthesis of 2-deoxy-D-ribose from D-arabinal, albeit the yield was poor, and the method has been re-investigated by other workers (Meischeimer and Jung, *Ber.*, 1927, **60**, 1462; Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803; Levene, Mikeska, and Mori, *ibid.*, 1930, **85**, 785; Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836; Ohta and Makino, *Science*, 1951, **113**, 273). Attempts to prepare this sugar in improved yield showed that methyl 2 : 3-anhydro-β-D-riboside with hydrogen bromide (Kent, Stacey, and Wiggins, *J.*, 1949, 1232), hydrogen chloride, or lithium aluminium hydride (Allerton and Overend, *J.*, 1951, 1480) gives mainly derivatives of 3-deoxy-D-xylose rather than of 2-deoxy-D-ribose. Similar results were obtained in the L-series by Mukherjee and Todd (*J.*, 1947, 969). A novel synthesis involving condensation of D-erythrose with nitromethane was described by Overend, Stacey, and Wiggins (*J.*, 1949, 1358) and by Sowden (*J. Amer. Chem. Soc.*, 1949, **71**, 1897; 1950, **72**, 808; *Adv. Carbohydrate Chem.*, 1951, **6**, 315), the last author claiming an improved overall yield. Recently, Matsushima and Imanaga have synthesised 2-deoxy-D-ribose from D-ribulose through the 2-amino-2-deoxypentitol, the overall yield being about 3% (*Nature*, 1953, **171**, 475). Overend and Stacey (*J. Sci. Food Agric.*, 1950, **1**, 168) have reviewed the methods available for the synthesis of 2-deoxy-D-ribose and its derivatives and the difficulties involved.

This communication is concerned with a synthesis of 2-deoxy-D-ribose from 2 : 3-*O*-*iso*propylidene-D-glyceraldehyde and allylmagnesium bromide. The condensation, in ether, gave syrupy 1 : 2-*iso*propylidenedioxyhex-5-en-3-ol (I); on catalytic hydrogenation this gave (II), which after hydrolysis yielded a crystalline 1 : 2 : 3-trideoxyhexitol in high yield, thus suggesting asymmetric synthesis in the Grignard reaction. Since 2-deoxy-D-ribose was finally obtained it seems probable that (II) has the D-*erythro*-configuration and that (I) contains largely the D-*erythro*-isomer. Hydroxylation of (I) by means of hydrogen peroxide in the presence of *tert.*-butanol and osmium tetroxide gave a mixture from which


(I)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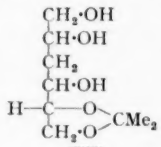
(III)

syrupy 3-deoxy-5 : 6-*O*-*iso*propylidenehexitol (III) was isolated in low yield. Raphael (*J.*, 1949, 544) has indicated the difficulty of hydroxylating terminal double bonds. Periodate oxidation of (III), followed by hydrolysis afforded a syrup which gave positive tests for 2-deoxypentose; paper chromatography suggested the presence of mainly 2-deoxyribose

with a little 2-deoxyxylose. The syrup gave a crystalline aniline derivative, identical with 2-deoxy-*N*-phenyl-D-ribosylamine, from which 2-deoxy-D-ribose was isolated. The poor overall yield renders the synthesis, in its present form, valueless as a preparative method.

## Experimental

Unless stated otherwise, distillations were under reduced pressure, paper chromatography was performed at 17° on Whatman No. 1 filter paper with *n*-butanol–ethanol–water (4 : 1 : 5 v/v) as mobile phase, and ammoniacal silver nitrate was used for the detection of polyhydric compounds on paper chromatograms (Hough, *loc. cit.*).

1 : 2-iso*Propylidenedioxyhex-5-en-3-ol.*—Allylmagnesium bromide was formed as described by Gilman and McGlumphy (*Bull. Soc. chim.*, 1928, **43**, 1322; see also Henze, Allen, and Leslie, *J. Org. Chem.*, 1942, **7**, 326) by slow addition of dry, redistilled allyl bromide (15·7 g.) to magnesium (15 g.) in dry ether (300 c.c.). The ethereal solution was rapidly filtered through a cotton-wool plug and to the filtrate was added an ethereal solution (50 c.c.) of freshly distilled 1 : 2-*O-iso*-propylidene-D-glyceraldehyde (Baer and Fischer, *J. Biol. Chem.*, 1939, **128**, 463) (8·3 g.). After 1 hour's stirring, ice and water (*ca.* 250 c.c.) were added, followed by 0·5N-sulphuric acid, dropwise with vigorous shaking, until the solution was faintly acid. The ethereal layer was separated, the aqueous phase was extracted with ether (2 × 250 c.c.), and the combined ethereal extracts were dried ($Na_2CO_3$) and evaporated, to give a pale yellow liquid (10·1 g.), $n_D^{15}$ 1·4520 (Found: C, 62·9; H, 9·3. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). Hydrolysis of a portion (2·56 g.) with 0·1N-sulphuric acid for 1 hr. at 95—100°, followed by neutralisation with barium carbonate and evaporation, gave syrupy *hex-5-ene-*1 : 2 : 3-*triol* (1·72 g.), $n_D^{20}$ 1·4835, $[\alpha]_D^{17}$ +4° (*c*, 2·46 in $CHCl_3$) (Found: C, 54·4; H, 9·0. $C_6H_{12}O_3$ requires C, 54·5; H, 9·1%). On oxidation with sodium metaperiodate, this consumed 2 mols. of periodate, forming one mol. of formic acid. It travelled as a single round spot ($R_F$ 0·72) on the paper chromatogram.

Hydrogenation of the syrupy *iso*propylidenedioxy-compound (0·43 g.) in methanol (20 c.c.) in the presence of Adams platinum catalyst (0·02 g.) at room temperature was complete in 5 hr. (1·06 $H_2$ consumed). The mixture was evaporated to a viscous syrup (0·48 g.), $[\alpha]_D^{17}$ +4° (*c*, 1·9 in $H_2O$). A portion (0·29 g.) was hydrolysed in 0·1N-sulphuric acid (15 c.c.) at 95—100° for 1 hr. and the mixture was neutralised with barium carbonate, filtered, and evaporated to a syrup, 1 : 2 : 3-*trideoxyhexitol* (0·22 g.), which crystallised spontaneously. The crystals, isolated on a tile and then recrystallised from ethanol, had m. p. 82°, $[\alpha]_D^{17}$ −4·5° (*c*, 1·8 in $H_2O$) (Found: C, 53·7; H, 10·4. $C_6H_{14}O_3$ requires C, 53·7; H, 10·4%). It gave one discrete spot ($R_F$ 0·76) on the paper chromatogram.

3-*Deoxy*-5 : 6-O-iso*propylidenehexitol* (III).—1 : 2-*iso*Propylidenedioxyhex-5-en-3-ol (I) (2·79 g.) was dissolved in *tert.*-butanol (30 c.c.), cooled to 0°, and mixed with a 0·5% solution of osmium tetroxide in *tert.*-butanol (1 c.c.). A 6·4% solution of hydrogen peroxide in *tert.*-butanol (10 c.c.) was added dropwise and the whole stored at 0° for 18 hr. (cf. Hackett, Sapp, and Millman, *J. Amer. Chem. Soc.*, 1941, **63**, 2051). The solution was evaporated in the presence of a little potassium carbonate, the residue was extracted with acetone (3 × 50 c.c.), and the extracts were evaporated to a dark brown syrup (3·16 g.). Paper chromatography showed it to be a mixture of at least four components ($R_F$ 0·85, 0·77, 0·66, and 0·03). Chromatography on a cellulose column with *n*-butanol–light petroleum (b. p. 80—100°) (40 : 60 v/v) as mobile phase (Hough, Jones, and Wadman, *J.*, 1950, 1702) gave a syrupy mixture of 3-deoxy-5 : 6-*O-iso*-propylidenehexitols {$R_F$ 0·77 and 0·66; 0·602 g.; $[\alpha]_D$ 0° (*c*, 3·4 in $H_2O$)} (Found: C, 52·6; H, 8·5. Calc. for $C_9H_{18}O_5$: C, 52·4; H, 8·7%). Examination on the paper chromatogram of the hydrolysis products of a little of the foregoing syrup revealed only one spot corresponding in position to that occupied by deoxyhexitols ($R_F$ 0·26).

2-*Deoxy*-D-*ribose.*—The deoxy-*O-iso*propylidenehexitols (III) (0·6 g.) were oxidised with sodium metaperiodate (20 c.c.; 0·17M) in a phosphate buffer (pH 7·4; 25 c.c.) at room temperature in the dark. After 2 hr., the solution was extracted with chloroform (3 × 75 c.c.), and the extract dried ($K_2CO_3$), filtered, and evaporated, to give a pale yellow syrup {0·34 g.; $[\alpha]_D^{17}$ −1° (*c*, 0·93 in $H_2O$)}. A portion (0·185 g.) was hydrolysed in 0·01N-sulphuric acid (25 c.c.) at 100° for 1 hr., whereafter $[\alpha]_D$ was constant (−19°). The solution was neutralised with barium carbonate, filtered, and evaporated to a syrup {0·134 g.; $[\alpha]_D^{17}$ −24·5° (*c*, 1·34 in $H_2O$)}, which gave positive tests for 2-deoxypentose with the Dische reagent (Dische, *Microchem. Acta*, 1930, **8**, 4; Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222; Overend, Shafidazeh, and Stacey, *J.*, 1950, 1027) and the Feulgen reagent (Feulgen, *Z. phys. Chem.*, 1923, **128**, 154;

1924, **135**, 203; Overend, *J.*, 1950, 2769). On the paper chromatogram it gave two spots corresponding to 2-deoxyribose ($R_F$ 0·32, strong spot) and 2-deoxyxylose ($R_F$ 0·36, weak spot).

After 5 hours' heating under reflux with alcoholic aniline (3·5%; 3 c.c.), the syrup (0·13 g.) gave 2-deoxy-*N*-phenylribosylamine (m. p. 161°) which on recrystallisation thrice from alcohol–ether had m. p. and mixed m. p. 171—172°, $[\alpha]_D^{17}$ +164° (*c*, 0·5 in pyridine; 10 min.) ⟶ + 64° (20 hr., const.) (63 mg.) (Found: C, 63·2; H, 6·9; N, 7·0. Calc. for $C_{11}H_{15}O_3N$: C, 63·2; H, 7·2; N, 6·7%). An *X*-ray powder photograph of the crystals was identical with that of an authentic specimen.

Hydrolysis of the aniline derivative (0·18 g.) (Overend, Stacey, and Wiggins, *J.*, 1949, 1358) gave a syrup {48 mg.; $[\alpha]_D$ −49° (*c*, 2·1)} which gave only one spot corresponding to 2-deoxyribose on the paper chromatogram; crystallised from *iso*propanol, it had m. p. 83—85°, $[\alpha]_D^{17}$ −55° (*c*, 0·96 in $H_2O$).

The author is indebted to Dr. J. K. N. Jones for his interest and advice.

THE UNIVERSITY, BRISTOL. [*Received, June 24th,* 1953.

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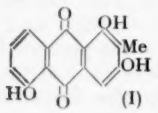
## 611. *Chemistry of the* Coprosma *Genus. Part VII.* A Revised Constitution for Lucidin.*

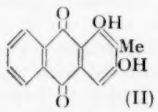
By LINDSAY H. BRIGGS and G. A. NICHOLLS.

By consideration of the infra-red spectrum and reconsideration of known properties the constitution of lucidin has been revised to 1 : 3-dihydroxy-2-hydroxymethylanthraquinone.

IN Part IV (*J.*, 1949, 1241) structure (I) was suggested for lucidin. The compound afforded a triacetate and a tribenzoate, indicating three hydroxyl groups. An alleged "trimethyl ether," formed by the action of methyl sulphate and potassium carbonate, further showed that all the hydroxyl groups were phenolic. A positive *C*-methyl determination (Found: 4·7; theory, 10·0%) indicated the presence of one such group, placed in the β-position after the isolation of 2-methylanthracene on distillation of lucidin with zinc. Further evidence was given for the position of the three hydroxyl groups, one significant fact being that the ultra-violet absorption maxima of lucidin and rubiadin (II), in alcohol and in concentrated sulphuric acid solution, were at exactly the same wave-lengths and differed only slightly in the degree of absorption.



(I)



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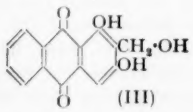


(III)

In Part VI (*loc. cit.*) consideration of the ultra-violet absorption spectra of a number of related anthraquinone compounds showed that the main carbonyl band was greatly affected by the presence of α-hydroxyl groups, β-hydroxyl groups having little effect. Compounds with one α-hydroxyl group had a carbonyl band at *ca.* 410 mμ, while those with two α-hydroxyl groups exhibited a band at *ca.* 430 mμ. In further agreement with this, rubiadin, with one α-hydroxyl group, has a maximum at 415 mμ.

Lucidin, however, exhibits maxima identical in wave-length with those of rubiadin and, on this basis, should possess only one α-hydroxyl group and not two as suggested.

In order to reconcile these facts, the *C*-methyl determinations were repeated, with negative results. Since a methyl group, therefore, does not occur in lucidin but appears after distillation with zinc, this leads to the formulation of lucidin as (III), which fits all the known facts.

The formations of the triacetate, tribenzoate, and the monomethyl ether (lucidin 3-methyl ether) obtained as a by-product on methylation, and the great similarity between the

* Part VI, *J.*, 1952, 1718.

absorption spectra of lucidin and rubiadin are now fully explained on this formula. The alleged " trimethyl ether," m. p. 173°, is, however, the *dimethyl ether* (*lucidin* 1 : 3-*dimethyl ether*), the alcoholic group remaining free (Found : C, 68·2; H, 5·05; OMe, 22·1, 22·5. New results : C, 68·4; H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7; 2OMe, 20·8%).

The infra-red absorption spectra of lucidin and its ethers confirm the new formula. Lucidin, above the 1600-cm.$^{-1}$ region, exhibits maxima at 3448, 3367, 1667, and 1621 cm.$^{-1}$. The first two bands are assigned to the alcoholic and β-hydroxyl groups but it is not possible to distinguish between them. The band at 1667 cm.$^{-1}$ is assigned to the unassociated carbonyl group while the band at 1621 cm.$^{-1}$ is assigned to the carbonyl group co-ordinated with the α-hydroxyl group (cf. Flett, *J.*, 1948, 1441, and forthcoming communication). Lucidin 3-methyl ether in the same region exhibits maxima at 3521, 1658, and 1629 cm.$^{-1}$. The first band is assigned to the alcoholic group, the second to the unassociated carbonyl group and the third to the co-ordinated carbonyl group. Lucidin 1 : 3-dimethyl ether in the same region exhibits maxima only at 3279 and 1669 cm.$^{-1}$, assigned to the alcoholic group and an unassociated carbonyl group respectively.

The further analyses are by Drs. Weiler and Strauss, Oxford, and Mr. R. N. Seelye of this College. We are greatly indebted to Dr. B. Cleverley for the infra-red measurements. Assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand and the Research Fund Committee of the University of New Zealand is gratefully acknowledged. One of us (G. A. N.) is indebted to the University of New Zealand for a Research Fund Fellowship.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, March 17th,* 1953.]

## 612. *The Colouring Matters of the Bark of* Rhamnus alaternus *L.*

By LINDSAY H. BRIGGS, F. E. JACOMBS, and G. A. NICHOLLS.

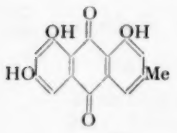
Two colouring matters, emodin and a new tetrahydroxymethylanthraquinone, probably the 3 : 4 : 5 : 7-tetrahydroxy-2-methyl compound, have been isolated from the hydrolysed extract of this bark.

*Rhamnus alaternus* L. has already been examined for hydroxyanthraquinones (Maurin, *Bull. Sci. pharmacol.*, 1924, **31**, 135; Vutyrakis, *Ann. Fac. franç. méd. pharm. Beyrouth*, 1937, **6**, 257; Olaechea, *Rev. Fac. Cienc. quím. La Plata*, 1945, **20**, 229; Marangoni, *Boll. Soc. Ital. Biol. sperim.*, 1946, **21**, 262; Raimondi, *Fitoterapia*, 1947, **18**, No. 3, 1) but, so far, only emodin (I) has been isolated (cf. Vutyrakis, *loc. cit.*). The tree is endemic to the Mediterranean countries but now grows wild in parts of New Zealand.

After preliminary extraction of the dried bark with light petroleum, exhaustive extraction with acetone yielded up to 22% of partly crystalline material consisting apparently of water-soluble hydroxyanthraquinone glycosides. Separation of this material into its constituents by chromatography was not readily achieved but the mixture of aglycones obtained after hydrolysis could be readily separated by chromatography on magnesia columns by the displacement technique (Briggs and Nicholls, *J.*, 1949, 1241). The chromatogram consisted of two main bands and a series of smaller bands (amounting to less than 1% of the total length). From the lower main band emodin (I) was isolated and, from the top purple band, a new tetrahydroxymethylanthraquinone, $C_{15}H_{10}O_6$. The latter formed a tetra-acetate and a tetramethyl ether, by the action of methyl sulphate and potassium carbonate in acetone solution, indicating that the four hydroxyl groups are phenolic. As a by-product in the methylation, a dimethyl ether was obtained; we therefore conclude that two of the hydroxyl groups are β since β-hydroxyl are much more readily methylated than α-hydroxyl groups (cf. Perkin, *J.*, 1907, **91**, 2066). The two remaining α-hydroxyl groups must be in the 1 : 8-(or 4 : 5-)positions since the infra-red absorption spectrum exhibits bands at 1681 and 1613 cm.$^{-1}$, characteristic of an unco-ordinated carbonyl group and a carbonyl group co-ordinated with an α-hydroxyl group, respectively (Flett, *J.*, 1948, 1441, and forthcoming communication). The presence of a band at 431 mμ

(log ε 4·03) in the ultra-violet absorption spectrum is also in harmony with the presence of two α-hydroxyl groups. Emodin (I) also exhibits a peak at 438·5 mμ (log ε 4·05) characteristic of two α-hydroxyl groups, while the tetramethyl ether of the new anthraquinone has a peak at 367 mμ (log ε 3·80), characteristic of anthraquinones with no free α-hydroxyl groups (cf. Briggs, Nicholls, and Paterson, *J.*, 1952, 1718). A 1 : 8-(or 4 : 5-)structure is also to be expected on phytochemical grounds since all hydroxyanthraquinones isolated from the Rhamnaceae which contain at least two hydroxyl groups have them in the 1 : 8-(or 4 : 5-)positions (cf. Mayer and Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publ. Corp., New York, 1943, pp. 117—137). The above infra-red evidence excludes 1 : 5- and 1 : 4-dihydroxy-structures while 1 : 4-dihydroxy-structures are also excluded by the fact the anthraquinone does not exhibit the fluorescence characteristic of this grouping (Raistrick, Robinson, and Todd, *Biochem. J.*, 1934, **28**, 559).

The anthraquinone contains a methyl group (Kuhn–Roth determination); in all anthraquinones derived from plants this is in the β-position. If this methyl group is ignored there are 22 possible tetrahydroxyanthraquinones. Of these, ten are excluded because they do not contain two α- and two β-hydroxy groups; a further eight isomers containing either 1 : 4- or 1 : 5-dihydroxy-structures are eliminated by the infra-red evidence. Four isomers, (II), (III), (IV), and (V) remain. The tetrahydroxymethylanthraquinone does not give the Bargellini test for vicinal trihydroxy-groups (*Gazzetta*, 1919, **49**, ii, 47; see also Seshadri and Rao, *Proc. Indian Acad. Sci.*, 1943, **17**, *A*, 20; Briggs and Locker, *J.*, 1949, 2159) and is not oxidised in alkaline solution, thus eliminating (II). It has dyeing properties on mordanted wool and is not eluted by acetic acid from a magnesia column, both properties characteristic of vicinal dihydroxyanthraquinones, thus eliminating (V). 1 : 2 : 7 : 8-Tetrahydroxyanthraquinone (IV) is known (cf. Wöbling, *Ber.*, 1903, **36**, 2941;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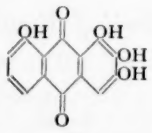
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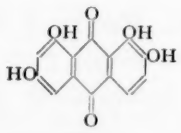
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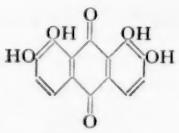
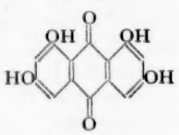
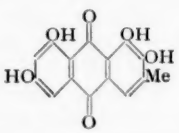

(IV)

Bistrzycki and Krauer, *Helv. Chim. Acta*, 1923, **6**, 769) and consists of red needles which give a blue colour in sodium hydroxide, a violet colour in sodium carbonate and ammonia solutions and a violet-red colour in concentrated sulphuric acid, becoming blue on the addition of boric anhydride. A β-methyl group would not be expected to have a great effect on these properties. The new anthraquinone, however, consists of brick-red plates giving red sodium hydroxide and concentrated sulphuric acid solutions. For these reasons we consider that (IV) can be eliminated, leaving the single possibility (III) for the tetrahydroxyanthraquinone. The methyl compound must then be a β-methyl derivative of (III), *i.e.*, (VI) or (VII).


(V)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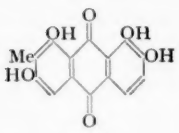
(VII)

Since (VI) represents a hydroxy-emodin, we consider that on phytochemical grounds (VI) best represents the new tetrahydroxyanthraquinone.

## Experimental

Some of the analyses are by Dr. T. S. Ma, Otago University, Dunedin, and Mr. R. N. Seelye of this department. We are indebted to Mr. R. M. L. Paterson for the absorption spectra recorded in this paper; they were measured in approximately 0·00005M-alcoholic solution with

a Beckman spectrophotometer, Model DU. We thank Dr. B. Cleverley for the measurement of the infra-red spectrum in a Nujol mull with a Beckman spectrophotometer, Model IR2.

The bark of a mature tree of *Rhamnus alaternus* L., growing on Rangitoto Island, was cut into small pieces, sun-dried, and ground to a powder. This was extracted exhaustively with light petroleum, which removed little, if any, of the colouring matters, and then with acetone in a Soxhlet apparatus; the extract was taken to dryness (yield, 22%). Chromatography of an acetone solution of this extracted material on a magnesia column was not satisfactory; two main bands were present but difficulties arose in the isolation of the water-soluble mixture of glycosides. When aqueous extracts of the two bands were poured into organic solvents only uncrystallisable oils were obtained. For these reasons our attention was directed to the aglycones.

The acetone extract almost completely dissolved in water, and the small amount of insoluble material was filtered off. For this reason, in proceeding directly to the aglycones, the preliminary extraction with light petroleum could be omitted. Concentrated hydrochloric acid was added to the aqueous solution (1 c.c. per 100 c.c. of water), which was then heated at 100° for 12 hr. The precipitate which formed on cooling was filtered off and washed with water until it was neutral (litmus) (yield of aglycone, 8%). The aglycone mixture was dissolved in acetone and chromatographed on freshly ignited magnesia; development with acetone was followed by displacement with acetic acid–acetone (cf. Briggs and Nicholls, *loc. cit.*) and further development with acetone for 18—24 hr. The chromatogram consisted of two main bands and a series of very small bands at the bottom. The pigments were recovered from the two main bands by dissolving the magnesia with hydrochloric acid and washing the residue with water until free from mineral salts. Each product was purified by rechromatographing it on 4 smaller columns of magnesia until a homogeneous chromatogram was obtained.

3 : 4 : 5 : 7-*Tetrahydroxy*-2-*methylanthraquinone*.—The pigment isolated from the purple band, which was not displaced by acetic acid, formed brick-red plates, m. p. 310° (constant; slow heating in a sealed tube), from glacial acetic acid (charcoal). It could also be purified by sublimation at 220°/0·01 mm. (Found: C, 62·6; H, 3·7; *C*-Me, 4·0. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5; *C*-Me, 5·2%). The *tetrahydroxymethylanthraquinone* exhibited maxima in the ultra-violet at 230·5, 284, 317·5, and 431 mμ (log ε 4·28, 4·41, 3·94, and 4·03, respectively), and in the infra-red at 3367, 1686, 1613, 1572, 1477, 1425, 1370, 1319, 1277, 1206, 1167, 1107, 1087, 1033, 995, 935, 886, 863, 826, and 759 cm.$^{-1}$, with an inflexion at 3195 cm.$^{-1}$.

*Tetra-acetate*. The anthraquinone (30 mg.) was acetylated with acetic anhydride (2 c.c.) and 60% perchloric acid (1 drop) during 1 hr. The product obtained on pouring the mixture into water was chromatographed in acetone on magnesia. The material recovered from the pink main band crystallised from glacial acetic acid in lemon-yellow needles, m. p. 224° (Found: C, 61·4; H, 3·9; Ac, 35·8. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0; 4Ac, 37·9%).

*Methylation*. The anthraquinone (203 mg.), in dry acetone (10 c.c.), was heated with methyl sulphate (1 c.c.) and anhydrous potassium carbonate (3 g.) for ½ hr. The mixture was poured into water, heated at 100° for ½ hr., and cooled, and the precipitate dissolved in acetone and chromatographed on magnesia. On development with acetone three bands and a coloured eluate were obtained. From the purple band unchanged anthraquinone was recovered. The material (30 mg.) isolated from the red band crystallised from glacial acetic acid (charcoal) in fine orange needles, m. p. 220° (constant; with sublimation) (Found: C, 65·3; H, 4·8; OMe, 24·5. The methoxyl determination was carried out on 1·563 mg., the only sample available, and is therefore not particularly accurate. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5; 2OMe, 19·7%). The *dimethyl ether* is insoluble in sodium carbonate solution but with sodium hydroxide solution a very insoluble dark red salt is formed. With concentrated sulphuric acid and ferric chloride solution it gives ruby red and brown colours respectively.

The *tetramethyl ether* (93 mg.), recovered from the eluate after evaporation of the solvent, crystallised from glacial acetic acid in yellow needles, m. p. 181—182° (Found: C, 66·4; H, 5·1. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·2%); it exhibited maxima at 225·5, 278, and 367 mμ (log ε 4·39, 4·45, and 3·80, respectively).

*Emodin*.—The pigment recovered from the red band of the main chromatogram could be purified either by sublimation at 175°/0·01 mm., followed by crystallisation from alcohol, or directly by crystallisation from glacial acetic acid (charcoal). Emodin was obtained in both cases as long orange needles, m. p. and mixed m. p. 255°. We are indebted to Professor Raistrick for an authentic specimen. The colour reactions in alkaline and sulphuric acid solutions were identical with those described for emodin while the triacetate, prepared with acetic anhydride and 60% perchloric acid, separated from glacial acetic acid in lemon-yellow

needles, m. p. 197° (Kögl and Postowsky, *Annalen*, 1925, **444**, 1, record m. p. 197° for this derivative). Emodin exhibited maxima in the ultra-violet at 253, 266, 289·5, and 438·5 mμ (log ε 4·23, 4·23, 4·29, and 4·05, respectively).

*Methylation.* A solution of emodin (55 mg.) in dry acetone (15 c.c.) was heated with methyl sulphate (1 c.c.) and anhydrous potassium carbonate (2 g.) for 15 min. at 100°. The mixture was cooled, filtered, and chromatographed on magnesia. After development with acetone, the chromatogram consisted of an orange small upper band, not readily eluted, a pale orange main band, and a pale yellow lower band. The material from the middle band crystallised from glacial acetic acid in orange-yellow needles, m. p. 201—202° [Raistrick, Robinson, and Todd, *J.*, 1937, 80, record m. p. 203—204° for emodin 7-methyl ether (physcion)].

In a similar experiment, in which the reaction time was 2 hr., the main band was the pale yellow one which was readily eluted. Emodin trimethyl ether was recovered from the eluate, and crystallised from glacial acetic acid in yellow needles, m. p. 222—223° (Oesterle and Tisza, *Arch. Pharm.*, 1908, **246**, 432, record m. p. 225°).

We are indebted to the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand and the Research Fund Committee of the University of New Zealand for grants. One of us (G. A. N.) also gratefully acknowledges the award of a Research Fund Fellowship.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, June 1st*, 1953.]

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## 613. *The Molecular Rotations of Polycyclic Compounds. Part II.* Diterpenoids and Sesquiterpenoids.*

By W. KLYNE.

The general method of molecular-rotation differences discussed in Part I * is used to correlate the stereochemistry of the diterpenoids and some sesquiterpenoids with that of the triterpenoids and the steroids. Conclusions for the A–B ring union in the diterpenoids agree with those previously reached on chemical grounds by Ruzicka, Jeger, and Lederer, and their colleagues.

The rotation contributions of conjugated diene types are discussed, and configurations at $C_{(13)}$ are allotted for abietic, lævopimaric, and *neo*abietic acids, and (provisionally) for some compounds of the manoöl–sclareol–agathenedicarboxylic acid group. Preliminary observations are made on the rotation contributions of five- and six-membered lactone rings. The sesquiterpenoids considered are those of decalin types which carry angle-methyl groups; they include the cyperones, selinene, eudesmol, and the "anomalous" compound eremophilone.

Suggestions for the nomenclature of the diterpenoids are made.

### DITERPENOIDS

*Nomenclature.*—The same general principles are applied as for steroids (*J.*, 1951, 3526) and triterpenoids (Halsall, Jones, and Meakins, *J.*, 1952, 2862).

*Fundamental hydrocarbons.* The names abietane, pimarane ($C_{20}$), and podocarpane ($C_{17}$) are allotted to the hydrocarbons (I), (II), and (III) respectively. Agathene and manoöl derivatives are named as derivatives of 7 : 8-*seco*pimarane (IV) for purposes of this paper.

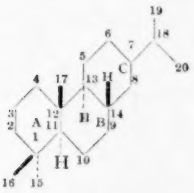
*Numbering.* This follows present practice for (I—III) (phenanthrene-type numbering).

*Lettering of rings.* This will be as shown in (I); in many previous papers the ring containing atoms 5—8 has been called B, but in view of the close relations between the diterpenoids and triterpenoids it seems better to denote corresponding rings in the same way.

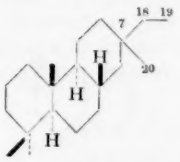
*Orientation of substituents.* This will be indicated by α and β, and broken and heavy lines respectively, as for steroids. It is shown in the present paper that the angle-methyl

* Part I, *J.*, 1952, 2916.

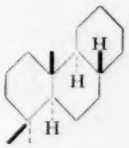
group at $C_{(12)}$ in the diterpenoids is oriented in the same way as the corresponding angle-methyl group at $C_{(10)}$ in the triterpenoids (V) and the steroids (VI). The numbering of rings A and B in the triterpenoids is now as in the steroids (*J.*, 1953, 3024).



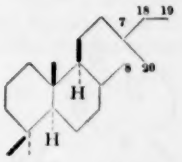
(I) Abietane



(II) Pimarane

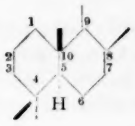


(III) Podocarpane

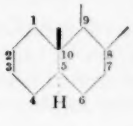


(IV) 7 : 8-*seco*Pimarane

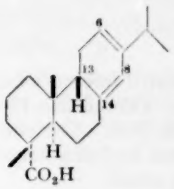
*Stereochemistry of ring-unions.* The stereochemistry of the (unknown) fundamental hydrocarbons (*trans-anti-trans*) is as shown in formulæ (I—III). If inversion has taken place at a ring junction, this will be indicated by a prefix giving the number of the carbon atom and the Greek letter α or β indicating the orientation of the hydrogen atom or substituent. Thus lævopimaric acid, shown below to be (VII), is named systematically 13β-abieta-6 : 8(14)-dien-15-oic acid.



(V)



(VI)



(VII)

*Points of stereochemistry as yet unknown.* Orientations at $C_{(7)}$ in many abietane, pimarane, and agathene derivatives, and at $C_{(13)}$ and $C_{(14)}$ in many pimarane and 7 : 8-*seco*-derivatives, are unknown. This is indicated by the use of ordinary lines for valency bonds to substituents, and the letter ξ in names, as required.

The author is indebted to the Editor of the *Journal* for helpful suggestions on these proposals.

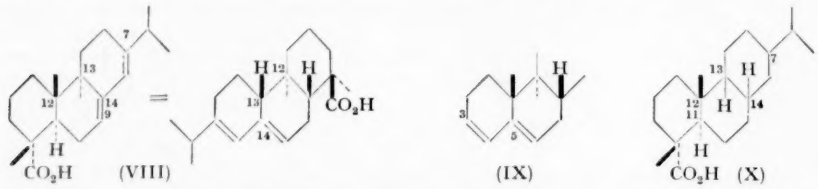
*General.*—Part I of this series (*J.*, 1952, 2916) described the general principles involved in the application of the method of molecular-rotation differences to the stereochemical correlation of polycyclic systems. It was shown that if present-day steroid conventions are used, as in (VI), the A–B ring union of the triterpenoids is of the same form as in (V). This correlation has been confirmed by Prelog *et al.* (*Helv. Chim. Acta*, 1953, **36**, 308, 320, 325), using the method of asymmetric synthesis. They have also shown that the steroid–triterpenoid convention and the glyceraldehyde convention are in agreement (cf. Mills, *J.*, 1952, 4976; *Chem. and Ind.*, 1953, 218).

Ruzicka, Jeger, and Lederer, and their colleagues have shown by purely chemical methods that the A–B ring union in the diterpenoids is of the same form as that in the triterpenoids and that it should therefore be written as in (I—III). (For summaries with references, see Barton, *Quart. Reviews*, 1949, **3**, 36, on diterpenoids; Jeger, *Fortschr. Chem. org. Naturstoffe*, 1950, **7**, 1, on triterpenoids.)

In the present paper the method of molecular-rotation differences will be applied to some stereochemical problems of the diterpenoids (and, to a smaller extent, the sesquiterpenoids) with particular reference to rotation differences associated with conjugated diene systems and aromatic nuclei. Experimental data, definitions, and conventions are as in Part I. $[M]_D$ values are shown in parentheses.

A very detailed review of the chemistry of the diterpenoids and sesquiterpenoids is given by Simonsen and Barton (" The Terpenes," Cambridge Univ. Press, 2nd edn., Vol. III, 1952). Shorter accounts are given by Barton (*loc. cit.*) and by Fieser and Fieser

("Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd edn., 1949). Where no references for rotation values are given in this paper, they may be found in one of these reviews. Rotations of steroids, where not stated otherwise, are taken from Part I (*loc. cit.*) or from Barton and Klyne (*Chem. and Ind.*, 1948, 755).

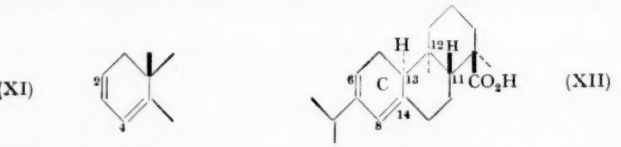



*Configurations at Ring Junctions.—Configurations at* $C_{(13)}$. Barton (*loc. cit.*) has suggested that in abietic acid [abieta-7 : 14(9)-dien-15-oic acid] the substituents at $C_{(13)}$ and $C_{(12)}$ are *trans* (VIII), since it is stable to acid whilst other isomers are not. This is supported by rotational evidence. If formula (VIII) is correct, abietic acid is an analogue of cholesta-3 : 5-diene (IX). The Δ values for the conjugated double bonds in these two compounds with reference to the corresponding saturated compounds are of the same sign and order of magnitude, which supports the formula (VIII).

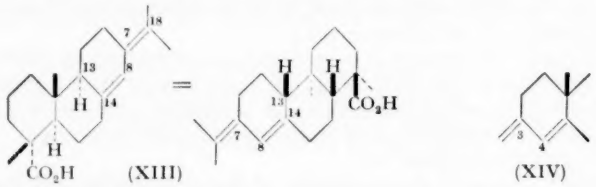
$$\Delta(\text{C:C–C:C in (VIII)}) = (-314°) - (+21°) = -335°$$
$$\Delta(\text{C:C–C:C in (IX)}) = (-458°) - (+91°) = -549°$$

The saturated reference compound used in the diterpenoid series is the tetrahydroabietic acid (7ξ : 13ξ : 14ξ-abietan-15-oic acid (X) (m. p. *ca.* 182°, Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 315). Comparisons in the steroid field (Klyne, *loc. cit.*, Table 4) show that with saturated hydrocarbons the difference in $[M]_D$ values between *cis*- and *trans*-decalin types is very small.

The same kind of reasoning shows that lævopimaric acid must be (VII) ($C_{(13)}$-H *cis* to $C_{(12)}$-Me) [13β-abieta-6 : 8(14)-dien-15-oic acid]. This compound on isomerisation with acid gives abietic acid; its configuration at $C_{(11)}$ and $C_{(12)}$ must therefore be the same as in (VIII). If the $C_{(13)}$-H in lævopimaric acid were *trans* to the $C_{(12)}$-methyl group, ring C of this acid would be of the same type as ring A of cholesta-2 : 4-diene (XI), which has a large




positive Δ value for the C:C–C:C grouping, *viz.*, $(+627°) - (+91°) = +536°$. Since lævopimaric acid has a large negative rotation (−830°) its C-ring must be enantiomeric to the A-ring of cholesta-2 : 4-diene, *i.e.*, the acid must be (VII), which may be rewritten as (XII) for comparison. This is contrary to the conclusion reached by Fieser and Fieser (*op. cit.*, pp. 74—75), who attempted to allot rotational contributions to individual carbon atoms. The present method of considering terminal ring-units seems preferable.

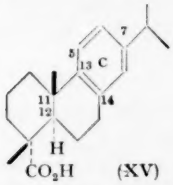



*neo*Abietic acid, obtained by Harris and Sanderson (*J. Amer. Chem. Soc.*, 1948, **70**, 339, 344), is very probably (XIII); its positive rotation (+480°) indicates that it must be of

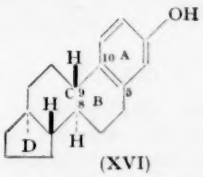
similar type to its nearest steroid analogue, the 3-methylenecholest-4-ene (XIV; +192°) of Musgrave (*J.*, 1951, 3121).

*Configurations at* $C_{(11)}$ *and* $C_{(12)}$. Rotational evidence is available which supports the purely chemical evidence cited above regarding the stereochemistry of $C_{(11)}$ and $C_{(12)}$.

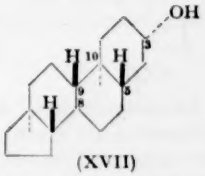
Dehydroabietic acid [abieta-5 : 7 : 14(13)-trien-15-oic acid] (XV; +186°) and tetrahydroabietic acid (7ξ : 13ξ : 14ξ-abietan-15-oic acid) (X; +21°) differ in that ring C is aromatic in (XV). The difference is similar to that between the steroids deoxo-œstrone and androstan-3β-ol which may be written as (XVI) and (XVII).



(XV)



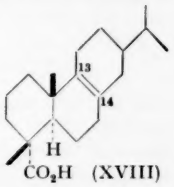
(XVI)



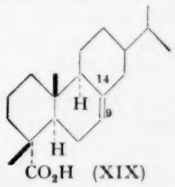
(XVII)

The Δ value for (XVI − XVII) which represents the effect of making ring A aromatic (ΔAr) is (+230°) − (+3°) = +227°. The ΔAr value for (XV − X) = (+186°) − (+21°) = +165°, which is of the sign and order of magnitude expected. Many dehydroabietic acids substituted in the aromatic ring are known (for a summary see Elsevier's "Encyclopaedia of Organic Chemistry," 1946, Vol. XIII, p. 961). These all have positive rotations, mostly differing from the rotation of the unsubstituted acid by not more than 50°.

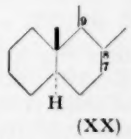
*Dihydroabietic acids.* Simonsen and Barton (*op. cit.*, p. 409) have suggested that Lombard's "β"- and "α"-dihydroabietic acids (*Bull. Soc. chim.*, 1942, **9**, 833; 1944, **11**, 526) may be the $\Delta^{13}$- and $\Delta^{9(14)}$-isomers (XVIII) and (XIX) respectively, since the compound (XVIII) with the ditertiary double bond would be the most stable.



(XVIII)



(XIX)



(XX)

The signs of the rotation differences between the dihydro-acids and the saturated tetrahydro-acid (+21°) support these suggestions. The two dihydro-acids are formally analogous to $\Delta^{8(9)}$- and $\Delta^{7}$-5α-steroids (cf. XX for numbering) respectively. Δ(C:C) values are :

| | | | |
|---|---|---|---|
| "β"-Dihydroabietic acid (XVIII ?) | *ca.* +350° | "α"-Dihydroabietic acid (XIX ?) ..... | −100° |
| $\Delta^{8(9)}$-5α-Steroid ..... | +100 | $\Delta^{7}$-5α-Steroid ..... | − 70 |

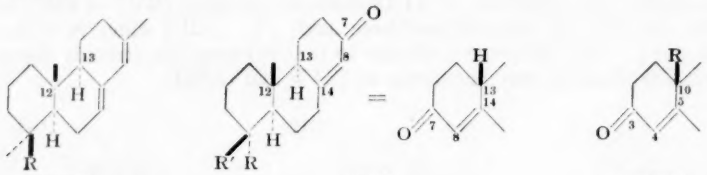
*Configurations at* $C_{(13)}$ *in the* 7 : 8-seco*pimaranes* (*agathenedicarboxylic acid, manoöl, sclareol group*). Chemical correlations by Ruzicka, Jeger, and Hosking, and their colleagues (for references see Barton and Jeger, *locc. cit.*) have shown that the stereochemistry of the union between the two rings of the agathenedicarboxylic acid, manoöl, and sclareol diterpenoids (7 : 8-*seco*pimaranes) is the same as that between the A- and the B-ring in abietic acid (cf. IV).

Rotational evidence (mentioned briefly by Barton, *loc. cit.*, p. 62) shows that certain degradation products of these 7 : 8-*seco*pimaranes have the hydrogen atom at $C_{(13)}$ *trans* to the angle-methyl group at $C_{(12)}$ [$C_{(13)}$α-H, as in (XXI)], although this is not rigid proof that the $C_{(13)}$-hydrogen atom is α in the original compounds.

The dienes (XXI; R = $CO_2Me$ or Me), from agathenedicarboxylic acid and manoöl respectively, have large negative rotations (−308°, −342°), which indicate that the $C_{(13)}$-hydrogen atom is α as in abietic acid (VIII) (−314°).

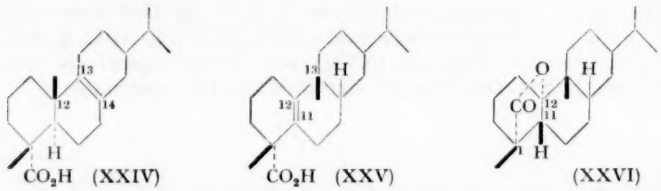
The unsaturated ketones (XXII; R = $CO_2Me$, R′ = Me, from *neo*abietic acid; and R = Me, R′ = $CO_2Me$, from agathenedicarboxylic acid) both have positive rotations

(+91° *, +142°) as would be expected if the $C_{(13)}$-hydrogen atom is α [compare cholest-4-en-3-one (XXIII; R = Me), for which Δ(C:C·C:O) is +266°; steroids not carrying a methyl group at $C_{(10)}$ (XXIII; R = H) have smaller positive Δ(C:C·C:O) values, *ca.* +150° (Klyne, *loc. cit.*)].



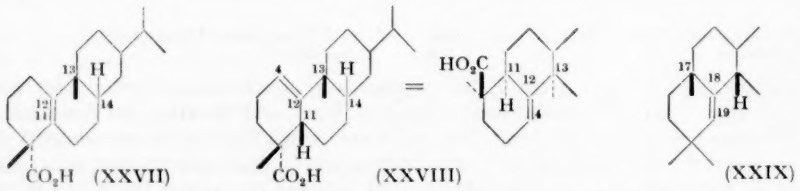
(XXI) (XXII) (XXIII)

*12-Nor-13-methylabietane derivatives.* Barton (*Chem. and Ind.*, 1948, **638**, where previous references are given) discussed the structure of the lactone $C_{20}H_{32}O_2$ (−6°) obtained from various dihydro-abietic and -lævopimaric acids (*e.g.*, XXIV) by treatment with strongly acidic reagents, and proposed for it the formula (XXVI) (12α-hydroxy-13β-methyl-12-nor-11β-abietan-15-oic lactone). He suggested that the lactone (XXVI) was formed from (XXIV) by a carbonium-ion rearrangement, the angle-methyl group moving from $C_{(12)}$ to $C_{(13)}$, followed by the formation of the $\Delta^{11(12)}$-acid (XXV), which then lactonised to (XXVI) with a β-hydrogen atom at $C_{(11)}$, " in order that the $C_{(1)}$-$CO_2H$ : $C_{(11)}$-H relationship may be changed from *cis* to *trans*."



(XXIV) (XXV) (XXVI)

When the lactone was treated with methylmagnesium iodide, two unsaturated acids [(−110°), m. p. 185—186°; and (+208°), m. p. 147—148°] were obtained. On the basis of their reactions with nitrosyl chloride or butyl nitrite, Simonsen and Barton (*op. cit.*, p. 410) allotted the formulæ (XXVII) and (XXVIII) to these acids respectively (stereochemistry at $C_{(14)}$ *not* indicated). (XXVII) is of a type enantiomeric to an 8(9)-unsaturated steroid and has the expected negative rotation (−110°) (cf. XX for numbering). The surroundings of the double bond in the isomer (XXVIII) are enantiomeric to those in the triterpenoid



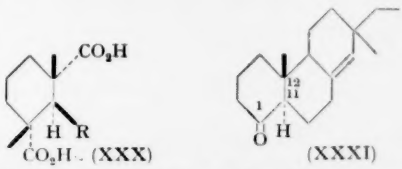
(XXVII) (XXVIII) (XXIX)

germanicol (XXIX); the Δ(C:C) value in the latter compound is negative (*ca.* −120°; Klyne, *loc. cit.*, Table 12); the rotation of (XXVIII) is positive (+208°) as expected on this analogy. It must be pointed out that the negative Δ(C:C) value of germanicol is anomalous, and no explanation of this anomaly can as yet be given.

*Dextropimaric acid.* The A–B ring union in this acid must be *trans* as in abietic acid, since both acids on vigorous oxidation give a mixture of two optically inactive tricarboxylic acids, $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_6$ (XXX; R = $CO_2H$ and $CH_2{\cdot}CO_2H$ respectively) (Ruzicka, de Graaff, Goldberg, and Frank, *Helv. Chim. Acta*, 1932, **15**, 915, and earlier references

* This value is an unpublished observation for which the author is indebted to Dr. G. C. Harris (cf. Harris and Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 339).

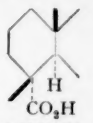
given there; Barton and Schmeidler, *J.*, 1948, 1197). That this ring union in dextropimaric acid is of the same *trans* type as in abietic acid is shown by the following evidence. Brossi and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2446) degraded dextropimaric acid to the ketone (XXXI) and the corresponding hydrocarbon. The positive Δ(C:O) value (+16°) shows that the A–B ring union in this compound is as shown in (XXXI), corresponding to abietic acid, the steroids, and triterpenoids. [This fact alone would not prove the configuration of the hydrogen atom at $C_{(11)}$ in dextropimaric acid, since (XXXI) is an α-decalone and might have rearranged at $C_{(11)}$.] The configuration at $C_{(13)}$ in dextropimaric acid (+220°) cannot be allotted with certainty, although it is probably α (cf. XXXII; R = ·CH:$CH_2$). The acid may be reduced to a dihydrodextropimaric acid (+60°) in




which the vinyl group has been reduced (Tschugaeff and Teearm, *Ber.*, 1913, **46**, 1769; Ruzicka and Bales, *Helv. Chim. Acta*, 1923, **6**, 677). The positive rotation of this dihydro-acid suggests that it is probably (XXXII; R = Et): this would be analogous to a $\Delta^4$-steroid which has a positive rotation. Reduction in more vigorous conditions ($PtO_2$ in acetic acid at 50°; Ruzicka, Huyser, and Seidel, *Rec. Trav. chim.*, 1928, **47**, 363) gives a mixture of tetrahydro-acids for which no rotation is given.

*Substituents.—Keto-groups in the* A- *and* B-*rings.* By analogy with the steroids and triterpenoids, it would be expected that diterpenoids carrying keto-groups in the A- and the B-rings would have positive and negative Δ(C:O) values respectively. This is borne out by the few diterpenoid ketones known. The Δ(C:O) values are as follows. A-Ring ketones: 3-ketomanoyl oxide (+76°); hinokione [keto-group probably at $C_{(3)}$ (Fieser and Fieser, *op. cit.*, p. 71), possibly at $C_{(2)}$ or $C_{(4)}$] (+192°); compound (XXXI) from dextropimaric acid (see above, +16°). B-Ring ketones: sugiol [6-hydroxyabieta-5 : 7 : 14(13)-trien-9-one) and its acetate (−57°, −105°)]; 9-ketohinokiol derivatives (four values, −25° to −100°; diketone −340°) (for references see Simonsen and Barton, *op. cit.*, pp. 359, 365—368, 372; Brandt and Thomas, *J.*, 1952, 2442).

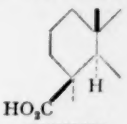
*Unsaturated compounds.* Subluskey *et al.* (to be published) have prepared several dehydroabietic acid derivatives containing an additional double bond at $C_{(9)}$:$C_{(10)}$, corresponding to $C_{(6)}$:$C_{(7)}$ in the steroids. The Δ(C:C) values of these compounds are negative, as expected on the analogy of $\Delta^6$-dehydro-œstrone [Δ(C:C-6), −770°] and similar compounds (Djerassi, Rosenkranz, *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4531, 4540).




(XXXIII)

Abietic acid and gypsogenin series

Less positive $[M]_D$



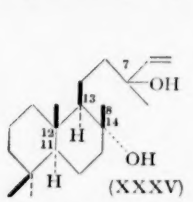

(XXXIV)

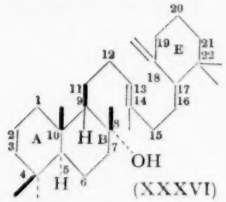
Podocarpic acid, agathenedicarboxylic acid, and α-boswellic acid series

More positive $[M]_D$

*Carboxyl groups at* $C_{(1)}$. Fieser and Fieser (*op. cit.*, p. 74) have pointed out that 1-carboxyl derivatives (XXXIII) of the abietic acid series are less dextrorotatory than the epimeric 1-carboxyl derivatives (XXXIV) of the podocarpic acid and agathenedicarboxylic acid series. (They use the terms α and β in the opposite sense to that used in this paper.) The configurations of the carboxyl groups in the diterpenoids being known (Barton, *loc. cit.*, p. 61), Vogel, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1951, **34**, 2321) have used optical-rotation evidence to correlate with these substances the stereochemistry of the functional groups at $C_{(4)}$ in certain triterpenoids (gypsogenin and α-boswellic acid).

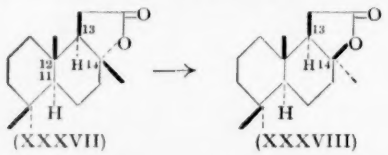
O-*Heterocyclic Derivatives.*—Five-membered lactone derivatives from sclareol (XXXV) are known; the same compounds and similar six-membered lactones have been obtained from the triterpenoid ambrein (XXXVI) (for a review see Jeger, *loc. cit.*). (XXXVI) conforms here with the new numbering for the pentacyclic triterpenoids; if it is written in this way the analogy between rings A and B and those of the pentacyclic triterpenoids

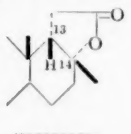

(XXXV)

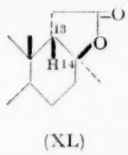

(XXXVI)

and the 7 : 8-*seco*pimaranes is clear. (Barton, *loc. cit.*, allots letters D and E to the bicyclic portion.)

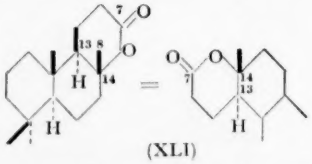
*Five-membered lactones.* If it is assumed—and this seems probable though not rigidly proved (see p. 3075)—that the $C_{(13)}$-hydrogen atom is α in the 7 : 8-*seco*pimaranes, the five-membered lactones of this group may be represented as follows. The lactone $C_{16}H_{26}O_2$ (XXXVII) is obtained by oxidation from sclareol (Ruzicka and Janot, *Helv. Chim. Acta*, 1931, **14**, 645; Ruzicka, Seidel, and Engel, *ibid.*, 1942, **25**, 621), and from ambrein (Lederer and Mercier, *Experientia*, 1947, **3**, 188). This lactone (+117°) is isomerised by ethanolic hydrogen bromide to another lactone (−30°) (presumably XXXVIII). This change is probably due to the rearrangement of a *trans*-fused system to a *cis*-fused system. *cis*-Fusion of a five-membered and a six-membered ring is more stable than *trans*-fusion for ketones and anhydrides (for a review see Linstead, *Ann. Reports*, 1935, **32**, 313).

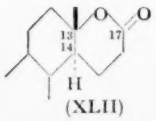

(XXXVII) (XXXVIII)


(XXXIX)


(XL)

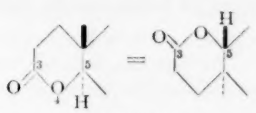
Consideration of the conformations of the decalin system in (XXXVII) and (XXXVIII) provides further indirect evidence for allotting the α-configuration to the hydrogen atom at $C_{(13)}$. If the $C_{(13)}$-H were β, the *cis*-lactone (XXXIX) could be formed readily. The *trans*-lactone (XL) *cannot* be formed if ring B is a chair form as usual; it can be formed only if ring B is a boat form and, whilst this is not impossible, it seems unlikely. Since (XXXVII) is obtained from sclareol without reaction at $C_{(13)}$ or $C_{(14)}$, the stereochemistry of the latter compound is very probably as in (XXXV), and that of ambrein must be similar.


(XLI)

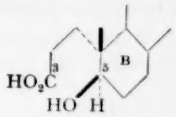

(XLII)

*Six-membered lactones.* As a result of the stereochemical arguments in the last section, the six-membered lactone, ambreinolide (+79°, +90°) obtained by Ruzicka and Lardon (*Helv. Chim. Acta*, 1946, **29**, 912) and by Lederer *et al.* (*ibid.*, p. 1354) from ambrein may be written as (XLI). This is of enantiomeric type to the D-ring lactones (XLII) obtained from 17-keto-steroids by oxidation with hydrogen peroxide in acetic acid. The latter compounds show a negative Δ value with reference to the corresponding saturated hydrocarbons—*e.g.*, the lactone from œstrone acetate (+138°) (Jacobsen, *J. Biol. Chem.*, 1947, **171**, 61); the corresponding hydrocarbon deoxo-œstrone (+227°); Δ value −89°.

Other related compounds are the 3-keto-4-oxasteroids (XLIII) described by Bolt (*Rec. Trav. chim.*, 1951, **70**, 940) (cf. Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579), which show large positive Δ values with reference to the corresponding saturated hydrocarbons (*e.g.*, 4-oxa-5α-cholestan-3-one, +345°, +312°; cholestane, +91°; Δ *ca.* +250°). Bolt states



(XLIII)



(XLIV)

that his compounds probably have the 5α-configuration shown in (XLIII). This seems certain, since the hydroxy-acids (XLIV) were obtained by reduction of the corresponding keto-acids with sodium and alcohol: this process is known to give equatorial hydroxy-groups (Barton, *Experientia*, 1950, **6**, 316), and the 5β-hydroxy-group is equatorial with reference to ring B.

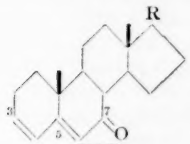
Turner (*loc. cit.*) obtained two 5-epimeric lactones by catalytic reduction of the corresponding 5-unsaturated enol lactone. His allotment of the 5α- and the 5β-configuration respectively to the isomers of higher and lower rotation [(+345°, +312°), m. p. 116°, and (+71°), m. p. 110°] was based on analogy with 5α-cholestan-3-one (+162°) and 5β-cholestan-3-one (coprostanone, +134°). This analogy seems a little dangerous, since we have no general knowledge of the effect of hetero-atoms on molecular rotations. Fortunately Turner's formulation is confirmed by the arguments above.

## Sesquiterpenoids

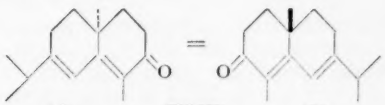
The sesquiterpenoids considered below are all of decalin types which carry angle-methyl groups, *viz.*, the cyperones, selinene, eudesmol, and the "anomalous" compound eremophilone. It is hoped to consider santonin, the alantolactones, and related compounds in a subsequent paper.

*Cyperones.*—Steroid **3**:5-dien-7-ones have very large negative rotations, *e.g.*, (XLV; R = $C_8H_{17}$) −1150° (Prelog, Ruzicka, and Stein, *Helv. Chim. Acta*, 1943, **26**, 2236) and (XLV; R = :O) −940° (Billeter and Miescher, *ibid.*, 1948, **31**, 629). **4**:6-Dien-3-ones have positive rotations, *e.g.*, methyl 3-ketoetia-4:6-dienate (+410°; Δ value, +248°) (Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003).

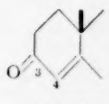
β-Cyperone (McQuillin, *J.*, 1951, 716) has a large positive rotation (+*745*°); it must therefore be written as (XLVI) in terms of steroid conventions. ([*M*]$_D$ values in italics are for the Hg 5461 Å green line).



(XLV)



(*A*) (XLVI) (*B*)



(XLVII)

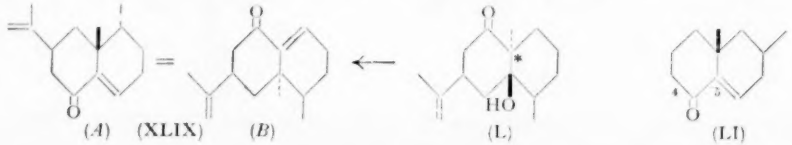
(XLVIII)

Steroid 4-en-3-ones (XLVII) have a large positive Δ value with reference to the corresponding saturated hydrocarbon (+266°). α-Cyperone, which can be transformed into β-cyperone (for references see McQuillin, *loc. cit.*), has a large positive rotation (+300°) in agreement with the formula (XLVIII). The corresponding tetrahydro-ketone has (+*33*°) (Simonsen and Barton, *op. cit.*, p. 205).

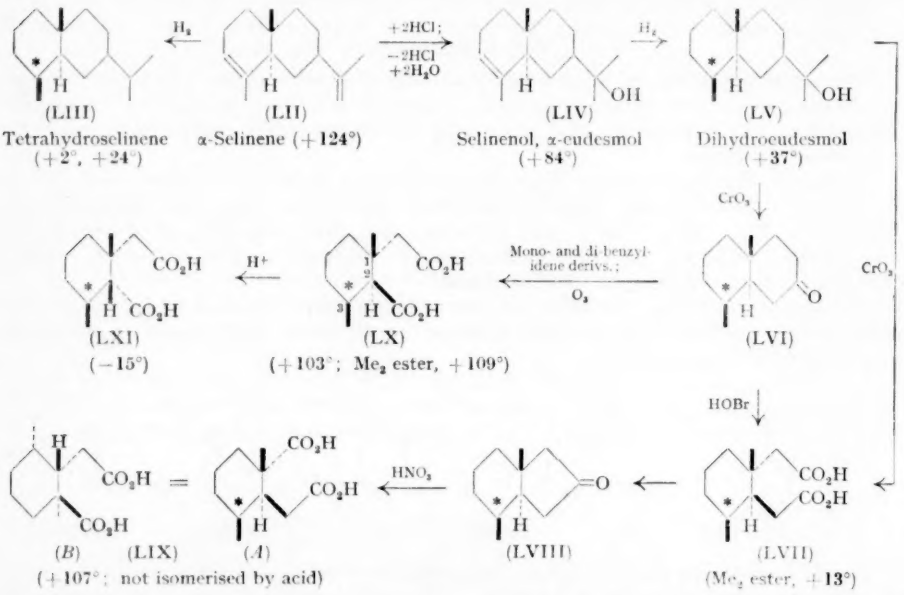
*Eremophilone.*—This ketone (XLIX) has a large negative rotation (−***451***°), in contrast to the tetrahydro-ketone (+*27*°) (Simonsen and Barton, *op. cit.*, pp. 212, 224). This indicates that eremophilone must be of the same stereochemical type as a steroid 5-en-4-one (LI). Butenandt and Ruhenstroh-Bauer (*Ber.*, 1944, **77**, 397) give (−123°) for cholest-5-en-4-one; the Δ value with reference to cholestane is (−214°).

Robinson (cf. Penfold and Simonsen, *J.*, 1939, 87) has suggested that eremophilone

(which does not fit the isoprene rule) might arise by dehydration and rearrangement of a structure such as (L) to (XLIX*B*). This imaginary precursor (L) has the same carbon skeleton as the cyperones (see, *e.g.*, XLVI*A*); the stereochemistry of the quaternary carbon atom (marked * in L) is the same in both cases. If the methyl attached to C* migrates, it should be α in (XLIX*B*)—as indeed the rotation of eremophilone shows it to be.



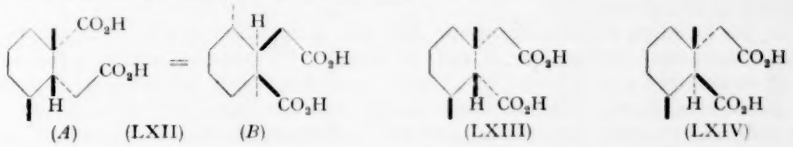

*Selinene–Eudesmol Group.*—Prof. D. H. R. Barton (personal communication to the author; cf. *Chem. and Ind.*, **1953**, **664**) has pointed out that a recent development of conformational analysis (Barton, *J.*, **1953**, **1027**) indicates that the decalin system in the selinene–eudesmol group is *trans*-fused, and not *cis*-fused as proposed by Ruzicka, Koolhaas, and Wind (*Helv. Chim. Acta*, **1931**, **14**, **1171**) on the basis of the physical properties of some derived hydrocarbons. Barton's suggestion is supported by a study of the rotations of some degradation products of eudesmol. Rotations also indicate that these compounds are of the same enantiomeric type as the cyperones. (In order to simplify the presentation of the argument, the correct stereochemical formulæ will be used from the start.)




The relevant degradations of selinene and eudesmol are summarised in formulæ (LII—LXI) (Ruzicka, Plattner, and Fürst, *ibid.*, 1942, **25**, 1364; Plattner, Fürst, and Hellerbach, *ibid.*, 1947, **30**, 2158). The isomerisation of 2-carboxy-1 : 3-dimethyl*cyclo*hexylacetic acid (LX to LXI) was at first thought to be a change from a *cis*- to a *trans*-arrangement of the acid substituents (Plattner *et al.*, *loc. cit.*). Barton (*Chem. and Ind.*, **1953**, **664**) has shown that the change must in fact be from *trans to cis*, his arguments depending on the justifiable assumption that the methyl group marked * in (LIII) and (LV—LXI) is almost certainly β since catalytic addition of hydrogen to selinene or eudesmol will take place more easily from the less hindered (α) side of the molecule.

The rotations of the dicarboxylic acids (LIX—LXI) support the conformational argument. If the decalin system in eudesmol were *cis*-fused, the acids (LIX—LXI) would become (LXII—LXIV) respectively.

Structures (LXII*B*) and (LXIII) are of enantiomeric types and should have rotations of opposite sign. Structures (LIX) and (LX) are of the same stereochemical type, differing only in the position of two methyl groups, as may be seen if (LIX*A*) is rewritten as (LIX*B*). The formulations of the two acids shown in the larger chart are supported by the fact that their rotations are almost identical.




(*A*) (LXII) (*B*) (LXIII) (LXIV)

Thus conformational and rotational analysis together indicate that eudesmol and selinene are *trans*-decalin derivatives. The allotment of the particular enantiomeric structures (with reference to the steroids) shown above is based on the Δ(C:C) values for the endocyclic double bonds in α-selinene and eudesmol. Both values are positive (approx. +100° and +47°; the Δ value for the side-chain double bond in $CMe{:}CH_2$ is small), and the compounds are therefore analogous to $\Delta^3$-steroids [Δ(C:C-3), +149°].

I am grateful to Prof. D. H. R. Barton for valuable discussions and comments on the manuscript. Parts of this paper were presented at the Gordon Research Conference of the American Association for the Advancement of Science at New Hampton, N.H., U.S.A., in August 1952. I am indebted to Dr. G. C. Harris, Dr. L. A. Subluskey, and their colleagues at the Hercules Experimental Station, Wilmington, Del., U.S.A., for a helpful discussion, and for some unpublished data.

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## 614. *Studies of Trifluoroacetic Acid. Part VIII.* Diazotisations of Aromatic Amines in Aqueous Trifluoroacetic Acid and Other Perhalogeno-carboxylic Acids.*

By M. R. Pettit, M. Stacey, and J. C. Tatlow.

Various aromatic amines, when diazotised in aqueous trifluoroacetic acid with sodium nitrite, give solid diazonium trifluoroacetates having the apparent formula $R{\cdot}N_2^+{-}O_2C{\cdot}CF_3{,}CF_3{\cdot}CO_2H$. Analogous salts are given by other acids, including heptafluorobutyric, trichloroacetic, and perfluoroadipic acids. Many of the acid salts may be kept for some time with little decomposition. They undergo the usual replacement and coupling reactions of diazonium salts in aqueous solution.

It was expected that diazotisation of aromatic amines would proceed normally in aqueous trifluoroacetic acid, since the latter is ionised to a considerable extent in dilute aqueous solution (Swarts, *Bull. Acad. roy. Belg.*, 1922, **8**, 343; Henne and Fox, *J. Amer. Chem. Soc.*, 1951, **73**, 2323). Normal reactions occurred with aniline, *p*-nitroaniline, and *p*-anisidine, the diazo-solution giving a good yield of the corresponding azo-β-naphthol coupling-product in each case. However, when *p*-toluidine, mesidine, 2 : 4-dimethyl-, *p*-chloro-, and *p*-bromo-aniline, in fairly concentrated trifluoroacetic acid solutions, were treated with aqueous sodium nitrite, colourless crystalline solids were deposited during the reactions. Addition of trifluoroacetic acid to aqueous toluene-*p*-diazonium chloride produced a lower layer from which a little of a similar solid crystallised. Solids were precipitated also, during diazotisations of aniline, *p*-toluidine, and *p*-chloroaniline in heptafluorobutyric acid,

* Part VII, *J.*, 1953, 735.

and of *p*-toluidine in trichloroacetic, perfluorohexanoic, tetrafluorosuccinic, and perfluoroadipic acids. Investigation showed that these solid derivatives were double salts, each containing a free acid molecule as well as the diazonium carboxylate; analysis and equivalent weight determinations suggested the general formula $R{\cdot}N_2^{+-}O_2C{\cdot}R',R'{\cdot}CO_2H$. Cryoscopic determinations on aqueous solutions (*ca.* 2%) of the acid trifluoroacetates of diazotised *p*-toluidine and mesidine revealed that about 3·8 g.-ions were present per g-equiv. of the salts. Goldschmidt (*Ber.*, 1890, **23**, 3220) has shown, by depression of the freezing point of water, that diazonium salts of mineral acids are dissociated almost completely in dilute solutions.

After the isolation of each diazonium acid salt, β-naphthol in alkali was added to the combined aqueous mother-liquors and washings. The corresponding azo-β-naphthol coupling-derivatives were isolated in all cases, in yields which, in conjunction with those of the solid salts, showed that the diazotisations had been complete or nearly so.

In general, the solid diazonium salts were relatively soluble in water and in polar organic solvents such as ethyl alcohol, acetone, and dioxan, and almost insoluble in non-polar organic solvents such as benzene, ether, light petroleum, chloroform, etc. In the solid state the salts were stable in the cold, and most were but little affected by being stored for several weeks. None has detonated even on being struck, although obviously, until more is known of their properties, care should be exercised in handling them. Each salt has a definite melting point, which is usually low, and at that temperature decomposition, vigorous but not apparently explosive, occurs. The bonding of the free acids in the acid salts appears to be weak, although all the salts were dried for several hours at 15° *in vacuo* over phosphoric oxide with no obvious decomposition. Similar drying for a week over phosphoric oxide or sodium hydroxide caused only a small increase in the equivalent. When mesitylenediazonium acid trifluoroacetate was washed with wet ether a significant increase (*ca.* 20%) in the equivalent was observed.

In aqueous solution, the acid salts exhibited the usual reactions of diazonium salts, and a number of replacement and coupling reactions of the diazonium groups of the aryl components were carried out. These proceeded smoothly and the expected products were obtained in good yields.

Stable solid diazo-compounds are well known, the most common being stabilised as complex salts with metallic halides, etc., with complex anions (*e.g.*, fluoroborate), or as salts of arylsulphonic acids (Saunders, "The Aromatic Diazo-compounds and their Technical Applications," Arnold, London, 1947, p. 69). It appears, however, that few acid salts of the general type reported herein have been described. Water-soluble double salts of diazonium chlorides and hydrogen chloride are known (Hirsch, *Ber.*, 1897, **30**, 1148; Hantzsch, *ibid.*, p. 1153) but these usually are of the form $(ArN_2Cl)_3,HCl$, only a few having equimolar proportions of acid. Hydrated diazonium acid fluorides have been reported also (Hantzsch and Vock, *Ber.*, 1903, **36**, 2059). For these salts Hantzsch at first postulated a structure involving two triply-bound quinquecovalent nitrogen atoms but later suggested that the acid was loosely attached (*Ber.*, 1930, **63**, 1786). Trifluoroacetic acid and other perfluoro-acids are known to form addition complexes, apparently of definite composition, with ethers and tertiary amines (Hauptschein and Grosse, *J. Amer. Chem. Soc.*, 1951, **73**, 5139). The double diazonium–perhalogeno-acid salts are virtually completely dissociated in solution and the binding forces are thus weak.

## Experimental

*Preparation of Diazonium Acid Salts.*—To a mixture of the amine, a small volume of water, and the perhalogeno-acid (about 3 equiv. proportions) at 0—5° was added a concentrated aqueous solution (*ca.* 40%) of sodium nitrite until a very slight excess was present (starch–iodide test). In general, a precipitate appeared as the diazotisation proceeded; when the amine salt was not completely soluble, the precipitate usually changed its crystalline form during the reaction, conversion into the diazonium salt being complete. The precipitate was filtered off, washed with small quantities of ice-cold water, and dried, finally for several hours *in vacuo* at 15° over phosphoric oxide. Equivalents were determined by titration in aqueous solution against standard alkali.

The mother-liquors and washings were combined, and treated with β-naphthol in aqueous sodium hydroxide; the precipitated azo-β-naphthol derivative was filtered off, washed, dried, and recrystallised, usually from ethyl alcohol or from acetone.

Details of the *diazonium acid salts* prepared are given in the Table. It is probable that higher yields could be obtained in many cases by using more concentrated solutions and less wash-liquid.

*Preparation of diazonium acid salts.*

| | Amine | | Acid, $R{\cdot}CO_2H$ | | $H_2O$ | $NaNO_2$ | Acid salt | |
|---|---|---|---|---|---|---|---|---|
| No. | Formula | g. | R | g. | (c.c.) | (g.) | g. | M. p. (decomp.) |
| I | *p*-$C_6H_4Me{\cdot}NH_2$ ..... | 3·32 | $CF_3$ | 10·7 | 13·0 | 2·38 | 5·40 | 70—72° |
| II | *sym.*-$Me_3C_6H_2{\cdot}NH_2$ ... | 1·13 | $CF_3$ | 3·0 | 6·0 | 0·68 | 1·04 | 65 |
| III | 2 : 4 : 1-$C_6H_3Me_2{\cdot}NH_2$ | 1·10 | $CF_3$ | 3·0 | 2·0 | 0·73 | 0·35 | 68 |
| IV | *p*-$C_6H_4Cl{\cdot}NH_2$ ..... | 2·50 | $CF_3$ | 8·9 | 2·0 | 1·55 | 2·53 | 71 |
| V | *p*-$C_6H_4Br{\cdot}NH_2$ ..... | 3·68 | $CF_3$ | 8·9 | 6·0 | 1·73 | 3·11 | 66 |
| VI | *p*-$C_6H_4Me{\cdot}NH_2$ ..... | 1·06 | $C_3F_7$ | 6·5 | 12·0 | 0·83 | 4·11 | 50—53 |
| VII | $NH_2Ph$ ..... | 0·49 | $C_3F_7$ | 3·4 | 1·5 | 0·43 | 1·45 | 31—34 |
| VIII | *p*-$C_6H_4Cl{\cdot}NH_2$ ..... | 0·67 | $C_3F_7$ | 3·8 | 2·0 | 0·46 | 2·27 | 75 |
| IX | *p*-$C_6H_4Me{\cdot}NH_2$ ..... | 2·64 | $CCl_3$ | 13·0 | 10·0 | 2·10 | 9·15 | 88 |

| | Acid salt | Required | | | Found | | | Azo-β-naphthol deriv. | |
|---|---|---|---|---|---|---|---|---|---|
| No. | Formula | C (%) | H (%) | Equiv. | C (%) | H (%) | Equiv. | g. | M. p. |
| I | $C_{11}H_8O_4N_2F_6$ [f] ... | 38·2 | 2·3 | 346 | 38·4 | 2·5 | 348 | 3·19 | 133—135° [a] |
| II | $C_{13}H_{12}O_4N_2F_6$ ... | 41·7 | 3·2 | 374 | 42·0 | 3·5 | 384 | 1·29 | 134—135 [b] |
| III | $C_{12}H_{10}O_4N_2F_6$ ... | 40·0 | 2·8 | 360 | 40·3 | 2·7 | 359 | 1·78 | 163 [c] |
| IV | $C_{10}H_5O_4N_2ClF_6$ [g] | 32·8 | 1·4 | 367 | 33·0 | 1·6 | 374 | 2·76 | 160—161 [d] |
| V | $C_{10}H_5O_4N_2BrF_6$ | 29·2 | 1·2 | 411 | 29·3 | 1·1 | 419 | 3·92 | 169—171 [e] |
| VI | $C_{15}H_8O_4N_2F_{14}$ ... | 33·0 | 1·5 | 546 | 33·2 | 1·4 | 556 | 0·47 | 131—133 [a] |
| VII | $C_{14}H_6O_4N_2F_{14}$ ... | 31·6 | 1·1 | — | 31·6 | 1·3 | — | 0·43 | 132—133 [a] |
| VIII | $C_{14}H_5O_4N_2ClF_{14}$ | 29·7 | 0·9 | 567 | 29·9 | 0·7 | 568 | 0·25 | 161 [d] |
| IX | $C_{11}H_8O_4N_2Cl_6$ ... | 29·7 | 1·8 | 445 | 29·7 | 1·8 | 445 | 0·63 | 133 [a] |

[a] Also mixed m. p. [b] Found: C, 78·4; H, 6·3. Calc. for $C_{19}H_{18}ON_2$: C, 78·6; H, 6·2%. Bourne, Stacey, Tatlow, and Tedder (*J.*, 1952, 1695) gave m. p. 131—133°. [c] Norman (*J.*, 1919, **115**, 673, gave m. p. 166°. [d] Meldola and Streatfeild (*J.*, 1888, **53**, 664) gave m. p. 162·5°. [e] Bamberger (*Ber.*, 1895, **28**, 1218) gave m. p. 172—173°. [f] Found: F, 32·6. Required: F, 32·9%. [g] Found: F, 31·6. Required: F, 31·1%.

*Toluene*-p-*diazonium Perfluoroadipate.*—*p*-Toluidine (0·51 g.) with water (5·0 c.c.) containing perfluoroadipic acid (2·20 g.) (Tatlow and Worthington, *J.*, 1952, 1251) gave a precipitate. During diazotisation at 0—5° with sodium nitrite (0·44 g.) in water (1·0 c.c.) solid remained but changed in appearance. Filtration, washing, and drying afforded *toluene*-p-*diazonium perfluoroadipate* (1·00 g.), m. p. 100° (decomp.) (Found: C, 38·2; H, 1·6%; Equiv., 406. $C_{13}H_8O_4N_2F_8$ requires C, 38·2; H, 2·0%; Equiv., 408). The aqueous phase and washings gave, with alkaline β-naphthol, tolyl-*p*-azo-β-naphthol (0·42 g.), m. p. and mixed m. p. 132—133°.

*Properties of Diazonium Acid Salts.*—(a) *Toluene*-p-*diazonium acid trifluoroacetate.* At 15° this salt was moderately soluble in water, readily soluble in ethyl alcohol, acetone, and dioxan, and only very slightly soluble in benzene, ether, light petroleum, chloroform, and carbon tetrachloride.

Cryoscopic measurements on aqueous solutions (1—2%) gave f. p. depressions corresponding to a molecular weight of 90·5, *i.e.*, 3·8 g.-ions per g.-equiv. of the salt.

Addition of trifluoroacetic acid (3·0 c.c.) to a solution of toluene-*p*-diazonium chloride [prepared in the usual way from the amine (1·64 g.), concentrated hydrochloric acid (5·0 c.c.), water (2·0 c.c.), and sodium nitrite (1·18 g.) in water (5·0 c.c.)] produced a heavy lower layer. When cooled, this deposited colourless needles of the diazonium acid trifluoroacetate (0·089 g.).

An aqueous solution of the acid salt (3%) with β-naphthol in alkali gave tolyl-*p*-azo-β-naphthol (84%), m. p. and mixed m. p. 134—135°.

(b) *Mesitylenediazonium acid trifluoroacetate.* F. p. determinations of aqueous solutions (2—3%) of this salt indicated an apparent molecular weight of 98·5, corresponding to 3·8 g.-ions per g.-equiv. of salt. After the salt had been washed with undried ether the equivalent was 455 (cf. Hantzsch, *loc. cit.*, 1897, who found that almost all the free acid could be removed from the diazonium acid chlorides if they were washed with undried ether).

*Replacement and Coupling Reactions of the Diazo-groups of Diazonium Trifluoroacetates.*—The following are representative of conversions which can be effected by using standard techniques.

The amines (*ca.* 0·03 mol.) were diazotised at 0—5° by use of aqueous trifluoroacetic acid (approx. 0·09 mol., *ca.* 1·5N), concentrated aqueous sodium nitrite being added until a slight excess was present.

A solution of diazotised aniline, after 75 min. at 50° and 15 min. at 100°, afforded phenol (88%), m. p. 38—40°, b. p. 176—182°.

A solution of diazotised *p*-toluidine was treated with (*a*) an excess of aqueous potassium iodide (50%) to give *p*-iodotoluene (81%), m. p. 29—32°, b. p. 209—211°, and (*b*) cuprous cyanide, to give *p*-tolunitrile (70%), m. p. 26—28°, b. p. 213—215°.

Tetrazotised benzidine was treated with hypophosphorous acid (50%) at 15° for 4 hr., and at 100° for ½ hr., to give diphenyl (63%), m. p. and mixed m. p. 69°.

The amines from which solid salts were prepared (see above) could be diazotised in dilute perhalogeno-acids, the salts remaining in solution, and the azo-β-naphthol coupling derivatives prepared in good yield.

*o*-Aminobenzotrifluoride (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346) was diazotised and coupled with β-naphthol (pH 8—10), to give 1-*o*-trifluoromethylphenylazo-2-naphthol (60%), m. p. 155° (Found: C, 64·5; H, 3·2. Calc. for $C_{17}H_{11}ON_2F_3$: C, 64·5; H, 3·5%), for which Cartwright and Tatlow (*J.*, 1953, 1994) gave m. p. 157—158°.

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## 615. *Studies of* Aspergillus niger. *Part I. The Structure of the Polyglucosan synthesised by* Aspergillus niger 152.

By S. A. BARKER, E. J. BOURNE, and M. STACEY.

"Mycodextran," renamed "nigeran," an intracellular polysaccharide of *Aspergillus niger* (strain 152), is a unique, essentially unbranched polyglucosan, in which about half of the glucosidic linkages are α-1 : 4, and half α-1 : 3; a small proportion of 1 : 6-bonds also may be present. End-group assay revealed an average chain length of 300—350 anhydroglucose units. Most, if not all, of the α-1 : 4- and α-1 : 3-linkages are arranged alternately. The name "nigerose" is suggested for 3-*O*-α-D-glucopyranosyl-D-glucose.

IN 1914, Dox and Niedig (*J. Biol. Chem.*, 1914, **18**, 167) reported that a polyglucosan ("mycodextran"), having $[\alpha]_D^{20}$ +251° in 0·1N-sodium hydroxide, can be extracted from *Penicillium expansum* with hot water; it is deposited when the solution is cooled. A similar polysaccharide was isolated by Dox (*ibid.*, 1915, **20**, 83) from cultures of *Aspergillus niger*. The present paper describes studies, previously reported briefly (Barker, Bourne, and Stacey, *Chem. and Ind.*, 1952, 756), of a polyglucosan, which was probably identical with these aforementioned, and which had been synthesised from sucrose by *Aspergillus niger* (strain 152). Two samples (A and B) of the polysaccharide were kindly provided by Dr. J. L. Yuill; sample (A) was the material which had been deposited when four successive hot-water extracts of the washed mycelium had been combined and cooled, while sample (B) was a purer product derived from only the last two of four such extracts. Dr. Yuill had shown previously (*ibid.*, p. 755) that analyses of sample (B), which was free from nitrogenous and mineral matter, indicated a formula $(C_6H_{10}O_5)_n$.

Paper chromatographic analysis of a hydrolysate of sample (B) revealed a single aldose component; this had an $R_F$ value identical with that of glucose. The extent of the conversion into glucose, determined by cuprimetric titration, was 97—98%. Sample (B), which gave a triacetate with acetic anhydride in pyridine, had $[\alpha]_D^{16}$ +283° in N-sodium hydroxide, compared with +270° for sample (A); these are exceptionally high figures for polyglucosans.

Samples (A) and (B) were partially hydrolysed with sulphuric acid, and the products

were analysed by paper chromatography; in each case the probable sugar components were those shown in the Table; the numerical results in the Table are those obtained when the hydrolysate from sample (B) was fractionated with aqueous ethanol on a charcoal column (cf. Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677; Bailey, Whelan, and Peat, *J.*, 1950, 3692).

| Solvent used for elution | Wt. (g.) of product | $[\alpha]_D$ (equil.) in water | Probable sugar components (by paper chromatography) | Conversion (%) into glucose by acid |
|---|---|---|---|---|
| Water, 1200 c.c. ..... | 0·749 | +53° | Glucose | 100 |
| 5% Ethanol (1), 900 c.c. ... | 0·003 | — | *iso*Maltose, maltose | — |
| 5% Ethanol (2), 1000 c.c.... | 0·256 | +134 | Maltose, disaccharide (X) | 94 |
| 10% Ethanol, 550 c.c. ..... | 0·031 | +136 | Disaccharide (X) | — |
| 15% Ethanol, 1000 c.c. ... | 0·068 | +160 | Trisaccharide | 94 |
| 35% Ethanol, 400 c.c. ..... | 0·216 | +197 | Higher saccharides | 99 |

The monosaccharide fraction gave crystalline α-D-glucose in 49% yield, and from the residual syrup D-glucosazone, D-glucophenylosotriazole, and β-D-glucopyranose penta-acetate were obtained. The first 5% ethanol eluate contained two disaccharides, probably *iso*maltose and maltose; the former, which constituted <1% of the total disaccharides isolated, may have arisen from α-1 : 6-linked glucose units in the polysaccharide, or it may have been a reversion product. The two principal bioses produced were maltose (characterised as its β-octa-acetate), and a disaccharide (X) having an $R_F$ value almost identical with that of laminaribiose (3-*O*-β-D-glucopyranosyl-D-glucopyranose); its large equilibrium optical rotation supported the view that an α-glucosidic linkage was present. Three crystalline derivatives of (X) were prepared, namely, an octa-acetate, the phenylosazone, and the phenylosotriazole, the last two being identical with the corresponding derivatives of turanose. Thus (X) was 3-*O*-α-D-glucopyranosyl-D-glucose. [For proof that turanose is 3-*O*-α-D-glucopyranosyl-D-fructose see Hudson's review (*Adv. Carbohydrate Chem.*, 1946, **2**, 1).] Gakhokidze (*J. Gen. Chem., U.S.S.R.*, 1946, **16**, 1923; 1949, **19**, 571, 2100) claimed to have synthesised crystalline 3-*O*-α-D-glucopyranosyl-D-glucopyranose by condensing α-D-glucopyranose 2 : 3 : 4 : 6-tetra-acetate with 4 : 6-*O*-benzylidene-1 : 2-*O*-*iso*propylidene-D-glucopyranose, and then removing the protecting groups; he gave $[\alpha]_D^{18}$ +84·8° (in $H_2O$), but did not indicate whether this was the initial or equilibrium value (see Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27).

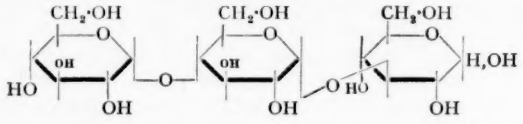
Methylations of samples (A) and (B) with sodium and methyl iodide in liquid ammonia afforded products with OMe, 44·6 and 45·0%, respectively (a tri-*O*-methylglucosan requires OMe, 45·6%). Filter-paper chromatography indicated that the two trimethyl ethers gave the same sugars when hydrolysed. In each case, there were two principal sugar components having $R_F$ values and staining properties with aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443) identical with those of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methyl-D-glucose. No di-*O*-methyl-D-glucose was detected, but a trace of a third component was shown, after being enriched by partition with chloroform, to be indistinguishable in its mobility from 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose. By use of the same partition technique, followed by quantitative assay on filter paper (Hirst, Hough, and Jones, *J.*, 1949, 928), the average chain length of the methyl ether of sample (A) was determined as *ca.* 300—350 glucose units. An approximate value of 175 glucose units was obtained when the degree of polymerisation of sample (B) was determined with an alkaline solution of 3 : 5-dinitrosalicylic acid (cf. Meyer, Bernfeld, Boissonnas, Gürtler, and Noelting, *J. Phys. Colloid Chem.*, 1949, **53**, 319). This lower figure may have been due, in part, to the known alkali-lability of reducing glucose units linked through position 3 (cf. Corbett, Kenner, and Richards, *Chem. and Ind.*, 1953, 154).

Fractional crystallisation of a hydrolysate of methylated sample (A) from ether afforded 2 : 4 : 6-tri-*O*-methyl-α-D-glucose; a further quantity of this sugar was recovered as its crystalline aniline derivative. The mother-liquors from this preparation, after being hydrolysed with acid, yielded 2 : 3 : 6-tri-*O*-methyl-α-D-glucose, which was isolated also as its αβ-1 : 4-bisphenylazobenzoate (cf. Coleman, Rees, Sundberg, and McCloskey, *J. Amer. Chem. Soc.*, 1945, **67**, 381). Since 2 : 3 : 6-tri-*O*-methyl-D-glucose differs from all other trimethyl ethers of glucopyranose in its ability to form a methylfuranoside, the

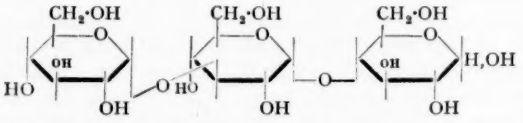
ratio of the two principal sugar derivatives in the hydrolysate of methylated sample (A) could be determined from measurements of the optical rotation of the mixture in cold 2% methanolic hydrogen chloride (cf. Granichstädten and Percival, *J.*, 1943, 54); the observed fall in the value of $[\alpha]_D$ from +70·8° to +22·6° corresponded to that shown by a mixture containing 47% of the 2 : 3 : 6-tri-*O*-methyl sugar.

Thus it was evident that, in the polyglucosan under examination, *ca.* 47% of the glucose units were linked through positions 1 and 4, and *ca.* 53% through positions 1 and 3. Hence, only *ca.* 47% of the units should have been susceptible to periodate oxidation, as was in fact confirmed subsequently, 0·47 and 0·48 molecular proportion of the oxidant being consumed per anhydroglucose unit in sample (B) after 44 and 92 hours, respectively. The periodate-resistant units yielded glucose on hydrolysis. The very small amount (*ca.* 0·03 molecular proportion per anhydroglucose unit) of formic acid liberated during the oxidation was consistent with this view, but no attempt was made to assess the chain length of the polysaccharide on this basis, because of (*a*) the difficulties inherent in determinations of such small amounts of the acid in the presence of other oxidation products, (*b*) dubiety concerning the number of mols. of formic acid liberated from the ends of an unbranched polysaccharide chain, and (*c*) the possibility that a small proportion of 1 : 6-linkages may have occurred in the polysaccharide (see above).

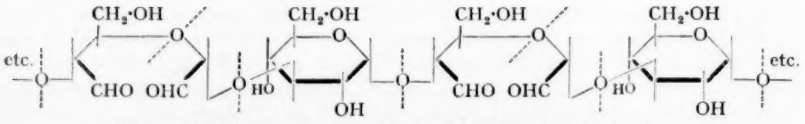
The failure of " mycodextran " to give a stain with iodine, and the resistance of the higher saccharides mentioned in the Table to both α- and β-amylase, revealed that the polysaccharide was not a mixture of amylose and an α-1 : 3-linked glucosan; moreover there could not have been any significant proportion of uninterrupted sequences of α-1 : 4-linkages more than *ca.* ten glucose units in length. As has been described by Bayly and Bourne (*Nature*, 1953, **171**, 385), the trisaccharide fraction mentioned in the Table was examined by the sensitive paper-chromatographic technique, involving conversion on the paper into its benzylamine derivative. The sole spot observed had an $R_F$ value intermediate between those of maltotriose and laminaritriose, so that the trisaccharide appeared to contain one 1 : 4- and one 1 : 3-link per molecule. Confirmation of this was obtained when partial hydrolysis of the trisaccharide yielded 3-*O*-α-D-glucosyl-D-glucose, maltose, and D-glucose. It was to be expected that the trisaccharide fraction contained two components, with the structures shown in (I) and (II), and indeed this was proved



(I)



(II)



(III) Broken lines signify points of rupture by phenylhydrazine.

in two ways. First, partial acidic hydrolysis of the hypoiodite-oxidised trisaccharide fraction yielded, *inter alia*, maltose and 3-*O*-α-D-glucosyl-D-glucose. Secondly, in collaboration with Dr. A. B. Foster, the two trisaccharides were separated by paper ionophoresis of their borate complexes, their $M_G$ values being compatible with the proposed structures (cf. Foster, *J.*, 1953, 982).

It thus appeared probable that a substantial proportion of the " mycodextran " mole-

cule contained α-D-glucopyranose units linked alternately through positions 3 and 4. Supplementary evidence in support of this conclusion was obtained when the periodate-oxidised polysaccharide (III) was treated with phenylhydrazine, a technique which has been used, for example, by Barry (*Nature*, 1943, **152**, 537) and by O'Colla (*Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 165) and is based on the fact that phenylhydrazine converts an acetal of glyoxal [$OHC{\cdot}CH(OR)_2$] into glyoxalosazone, with the liberation of the alcohol (ROH). From the mixture of osazones thus obtained, D-glucosazone was isolated in an overall yield from " mycodextran " of 22%; in the absence of any significant degree of branching, it must have arisen from glucose residues joined through positions 1 and 3 to two periodate-sensitive units. The absence of a polysaccharide osazone from the products eliminated any possibility that long sequences of α-1 : 3-linkages occur in " mycodextran."

" Mycodextran " bears a resemblance to Floridean starch ($[\alpha]_D$ +156° in $H_2O$), inasmuch as they both contain appreciable proportions of 1 : 3- and 1 : 4-glucosidic bonds (cf. Barry, Halsall, Hirst, and Jones, *J.*, 1949, 1468), but the former polysaccharide has a higher optical rotation, suggesting that a greater proportion of the linkages are in the α-form. It is now apparent that the " mycodextran " structure is markedly different from those of dextrans, in which the principal glucosidic linkages are of the α-1 : 6-type, so that the term " mycodextran " must inevitably lead to confusion. We suggest that the polysaccharide should now be known as " nigeran," and 3-*O*-α-D-glucopyranosyl-D-glucose as " nigerose."

## Experimental

*Isolation of " Mycodextran " (Nigeran).*—The polysaccharide, kindly supplied by Dr. J. L. Yuill, had been isolated from *Aspergillus niger* (strain 152), which had been grown on sucrose and washed thoroughly with cold water. The mycelium had been extracted with boiling water for 5 min., and the filtered extract cooled to precipitate the polysaccharide. Sample (A) was the product from four successive extracts, whereas sample (B) was obtained from the third and fourth extracts. Both samples had been washed with alcohol and then with ether, before being dried at 55—60°.

*Examination of Sample (B).*—(a) *Reducing power.* The method employed was essentially that described by Meyer *et al.* (*loc. cit.*). The reagent—3 : 5-dinitrosalicylic acid (1·5 g.) in 0·2N-sodium hydroxide (100 c.c.)—had been calibrated against maltose hydrate. The reagent (1 c.c.) was added to a solution of sample (B) (0·10 g.) in 2N-sodium hydroxide (3 c.c.), and the mixture was kept at 65° for 30 min., cooled, and diluted with water (20 c.c.), before the intensity of colour was determined. In order to correct for the turbidity of the polysaccharide solution, an extra blank containing no added reagent was treated similarly. The results indicated that the degree of polymerisation was *ca.* 175.

(b) *Reducing sugars liberated during acidic hydrolysis.* (i) *Identification.* Sample (B) (20 mg.) was kept at 100° for 5 hr. with 2N-sulphuric acid (1 c.c.) in a sealed tube; the solution was diluted with water (2 c.c.), and freed from ions by means of an apparatus similar to that described by Consden, Gordon, and Martin (*Biochem. J.*, 1947, **41**, 590). The hydrolysate, together with reference solutions, was separated on paper chromatograms, irrigated with the upper phase of a mixture of *n*-butanol (40%), ethanol (10%), water (49%), and ammonia (1%), for 24 hr. (solvent front retained on the paper) and 48 hr., respectively. Only one sugar component was revealed on development with aniline hydrogen phthalate (Partridge, *loc. cit.*), and this had an $R_F$ value identical with that of the glucose reference spot.

(ii) *Determination.* Sample (B) was hydrolysed for 6 hr. with 7% sulphuric acid at 100°, and the glucose produced was determined by cuprimetric titration, as described by Bourne, Donnison, Haworth, and Peat (*J.*, 1948, 1687). After a small correction (3%) had been applied for the loss in reducing power which occurs with glucose itself under these conditions (Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224), the reducing power of the neutral hydrolysate corresponded to a conversion into glucose of 97—98%.

(c) *Optical rotation.* The polysaccharide (B), although sparingly soluble in cold water, dissolved readily in hot water. It had $[\alpha]_D^{16}$ +283° (*c*, 0·78 in N-NaOH), compared with +270° (*c*, 1·04) for sample (A).

(d) *Iodine stain.* Sample (B) gave no detectable stain with iodine under the standard conditions for the determination of blue value (B.V.) described by Bourne, Haworth, Macey, and Peat (*J.*, 1948, 924).

*Partial Acidic Hydrolysis of the Polysaccharide.*—Sample (B) (1·363 g.) was partially hydrolysed with N-sulphuric acid (150 c.c.) at 85° for 3 hr. The hydrolysate then had $[\alpha]_D^{23}$ +121° (*c*, 0·68 in $H_2O$), and the reducing power corresponded to a 63·3% conversion into glucose. The saccharide mixture was fractionated on a charcoal column (17 × 3·4 cm.) by Whistler and Durso's method (*loc. cit.*). The column was washed as shown in the Table. Each of the eluates was neutralised with barium carbonate, concentrated to a small volume (*ca.* 25 c.c.), filtered, and freeze-dried to a white solid or a syrup, which was subsequently dried to constant weight at 60° in a vacuum over phosphoric oxide.

(a) D-*Glucose.* The product from the aqueous eluate, crystallised from methanol, gave α-D-glucose (0·365 g.), m. p. and mixed m. p. 139—142°, $[\alpha]_D^{17}$ +101·5° (2·5 min.) ⟶ +53·1° (equil.) (*c*, 0·85 in $H_2O$). From the mother-liquors D-glucosazone [m. p. and mixed m. p. 204—205° (decomp.)], D-glucophenylosotriazole (m. p. and mixed m. p. 195—197°), and β-D-glucose penta-acetate (m. p. and mixed m. p. 129—131°) were prepared.

(b) 3-O-α-D-*Glucopyranosyl*-D-*glucose* [*Disaccharide* (*X*)]. A duplicate experiment, carried out on a larger scale with sample (A), gave a 5% ethanol eluate rich in disaccharide (X), but contaminated with a trace of maltose. The freeze-dried solid (0·565 g.), phenylhydrazine (1·5 c.c.), glacial acetic acid (1·5 c.c.), and water (7·5 c.c.) were kept at 100° for 30 min., and cooled. Washed with water and crystallised from ethanol, the precipitate gave turanose phenylosazone (0·207 g.), m. p. and mixed m. p. 204—206° (Found : N, 11·0. Calc. for $C_{24}H_{32}O_9N_4$ : N, 10·8%). Other samples of the osazone were prepared similarly.

An aqueous solution (9 c.c.) of the osazone (0·306 g.) was heated on a boiling-water bath for 30 min. with cupric sulphate pentahydrate (0·440 g.), cooled, filtered, saturated with hydrogen sulphide, and filtered again. The filtrate was neutralised with barium carbonate, clarified, and extracted with ether to remove the aniline. The aqueous layer was concentrated to a syrup, which was crystallised from ethanol to give turanose phenylosotriazole (0·077 g.), m. p. and mixed m. p. 190—191° (Found : C, 50·6; H, 6·0; N, 9·6. Calc. for $C_{18}H_{25}O_9N_3$ : C, 50·6; H, 5·9; N, 9·8%). The osazone and the osotriazole gave infra-red spectra identical, over the range 700—960 $cm.^{-1}$, with those of authentic specimens.

Disaccharide (X) (0·041 g.) was heated with acetic anhydride (0·41 c.c.) and anhydrous sodium acetate (0·011 g.) at 100—110° for 70 min. Isolated in the usual way and crystallised from ethanol, the *acetate* (0·027 g.) had m. p. 111—113° (Found : C, 49·7; H, 5·65. $C_{28}H_{38}O_{19}$ requires C, 49·6; H, 5·6%).

A syrupy disaccharide fraction (0·470 g.), containing both maltose and disaccharide (X), treated with 4·3% methanolic hydrogen chloride (20 c.c.) at room temperature, showed $[\alpha]_D^{17}$ +126·4° (3 min.) ⟶ +89·8° (74 min.) ⟶ +85·8° (20 hr.), whereas, under the same conditions, maltose hydrate showed $[\alpha]_D^{17}$ +127·5° (3 min.) ⟶ +126·1° (74 min.) ⟶ +112·6° (19 hr.). Thus it was probable that disaccharide (X) carried a free hydroxyl group at position 4 of the reducing unit. It is likely that maltose and disaccharide (X) could be separated more efficiently by virtue of their markedly different rates of reaction with methanolic hydrogen chloride than on a charcoal column, and this possibility is being explored.

(c) *Maltose.* A disaccharide fraction (0·074 g.), relatively rich in maltose but contaminated with a trace of disaccharide (X), was kept with acetic anhydride (2 c.c.) in pyridine (2 c.c.) at room temperature for 24 hr., giving β-maltose octa-acetate (0·089 g.), m. p. and mixed m. p. 158—159°, $[\alpha]_D^{17}$ +64·6° (*c*, 0·42 in $CHCl_3$) (Found : C, 49·3; H, 5·7. Calc. for $C_{28}H_{38}O_{19}$ : C, 49·6; H, 5·6%).

(d) *Trisaccharide fraction.* The material eluted by 15% ethanol after partial hydrolysis of sample (B), was examined, as its benzylamine derivative (Bayly and Bourne, *loc. cit.*), on a paper chromatogram. Only one spot was revealed; it did not arise from *iso*maltotriose, laminaritriose, maltotriose, or panose. It had an $R_F$ value intermediate between those of the benzylamine derivatives of laminaritriose and maltotriose, which suggested that the trisaccharide fraction had a 1 : 3- and a 1 : 4-glucosidic bond. However, electrophoretic separation of the fraction, in borate buffer, on filter paper showed two components with mobilities similar to those of the α-1 : 3- and α-1 : 4-linked disaccharides (cf. Foster, *loc. cit.*).

Partial hydrolysis of the trisaccharide fraction (5 mg.) with N-sulphuric acid (1 c.c.) at 90° for 30 min. gave three products, having $R_F$ values identical with those of glucose, maltose, and 3-*O*-α-D-glucopyranosyl-D-glucose. Both disaccharides, *inter alia*, were again evident in a hydrolysate of hypoiodite-oxidised trisaccharide.

*Acetylation of Sample* (B).—The polysaccharide (95·2 mg.), acetic anhydride (2 c.c.), and pyridine (2 c.c.) were kept at room temperature for 48 hr. and then at 100° for 3 hr. The *acetate* (140·5 mg.) was precipitated with water, washed, and dried over phosphoric oxide at

60°/15 mm.; it had $[\alpha]_D^{17}$ +157° (*c*, 0·29 in $CHCl_3$) (Found: C, 50·3; H, 5·7. A tri-*O*-acetylglucosan $C_{12}H_{16}O_8$ requires C, 50·0; H, 5·6%).

*Methylation of Sample* (B).—The dried polysaccharide (0·935 g.) was treated with sodium and methyl iodide in liquid ammonia at −70° (cf. Freudenberg and Boppel, *Ber.*, 1938, **71**, 2505). After four additions of the methylating reagents had been made, the ammonia was allowed to evaporate under anhydrous conditions, the last traces being removed at 55°/15 mm. Extraction of the residue with chloroform (Soxhlet) gave, from the extract, a solid (1·088 g.) having $[\alpha]_D^{17}$ +198·7° (*c*, 0·40 in $CHCl_3$) (Found: OMe, 39·5. Calc. for a tri-*O*-methylglucosan $C_9H_{16}O_5$: OMe, 45·6%). Part (0·857 g.) of this material was treated with four more portions of the methylating reagents, and, after further treatment as above, the product was dialysed against several changes of distilled water, and the water-soluble *ether* was freeze-dried to a white solid (overall yield, 64%), $[\alpha]_D^{17}$ +217·8° (*c*, 0·70 in $CHCl_3$) (Found: OMe, 45·0%).

*Methylation of Sample* (A).—The polysaccharide (6·86 g.), purified by "crystallisation" from water, was methylated as above, eight additions of the methylating reagents being made. The product was suspended in water (150 c.c.), and extracted with chloroform (250 c.c.; 50 c.c.; 50 c.c.). The combined extracts were washed with water, filtered, and evaporated, the residue being ground with ether and dried to a white powder, from which impurities soluble in light petroleum (b. p. 60—80°) were removed in a Soxhlet apparatus. The overall yield was 67% (Found: OMe, 44·6%).

*Methanolysis and Hydrolysis of the Polysaccharide Ethers.*—(a) *Paper chromatographic analysis of the O-methylglucoses.* The methyl ether of sample (B) was submitted to methanolysis and then to hydrolysis with 4% hydrochloric acid. A paper chromatogram of the hydrolysate, freed from ionised impurities as above, was irrigated for 48 hr. as before, and sprayed with aniline hydrogen phthalate; it showed two principal spots, of approximately equal intensity, having colours and $R_F$ values identical with those of spots of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose (brown and red stains, respectively). They were distinguished from 2 : 3 : 4- and 2 : 3 : 5-tri-*O*-methylglucose on the same chromatogram; no di-*O*-methylglucose could be detected.

A similar result was obtained with the methyl ether of sample (A). In addition, an intense spot corresponding in colour, and in $R_F$ value, to 2 : 3 : 4 : 6-tetra-*O*-methylglucose was revealed after it had been enriched by chloroform–water partition.

(b) *End-group assay.* The methyl ether of sample (A) (0·488 g.) was treated for 7 hr. with boiling methanolic 8·7% hydrogen chloride (40 c.c.). The residue obtained when the solution was neutralised with lead carbonate, filtered, and evaporated, was hydrolysed with 4% hydrochloric acid (40 c.c.) at 100° for 6 hr. The aqueous solution was neutralised with lead carbonate, filtered, and evaporated, and the *O*-methylglucoses were extracted exhaustively with ether. The extracts yielded a syrup, which was dissolved in water (10 c.c.) and extracted with water-washed chloroform (9 × 10 c.c.). The combined extracts were washed with water (90 c.c.) before being concentrated to a syrup, in which the tri- and tetra-*O*-methylglucoses were determined according to the paper chromatographic procedure described by Hirst, Hough, and Jones (*loc. cit.*). The factors 1·62 and 825 were applied to give, respectively, the amounts of "tetra" and "tri" present before the enrichment process, and in this way two determinations gave chain lengths of 300 and 360 anhydroglucose units. [In these calculations, the partition coefficient of 2 : 3 : 4 : 6-tetra-*O*-methylglucose was assigned the value determined by Macdonald (*J. Amer. Chem. Soc.*, 1935, **57**, 771); it was assumed that 2 : 4 : 6-tri-*O*-methylglucose had the same partition coefficient as that determined for its 2 : 3 : 6-isomer by Macdonald.]

(c) *Characterisation of the tri-O-methylglucoses.* A solution of the methyl ether (1·722 g.) of sample (A) in methanolic 3% hydrogen chloride (100 c.c.) was kept at 80° for 10 hr., neutralised with lead carbonate, filtered, and evaporated. The glycosides were treated with aqueous 4% hydrochloric acid (85 c.c.) at 100° for 5 hr., and the solution was neutralised with lead carbonate, filtered, and evaporated. Crystallisation of the chloroform-soluble portion from ether gave needles of 2 : 4 : 6-tri-*O*-methyl-α-D-glucose (0·394 g.), m. p. and mixed m. p. 114·5—116·5°, $[\alpha]_D^{16}$ +105° (2·5 min.) ⟶ +72·5° (3 days) (*c*, 0·5 in $H_2O$), $[\alpha]_D^{16}$ +84·3° (1·5 min.) ⟶ +72·6° (7 days) (*c*, 0·4 in methanolic 2% hydrogen chloride) (Found: C, 48·6; H, 8·0. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2%). Lake and Peat (*J.*, 1938, 1417) gave m. p. 115°, $[\alpha]_D^{20}$ +98·2° ⟶ +74·8 (equil.) in $H_2O$.

The ethereal mother-liquors yielded a syrup (1·024 g.), which was boiled for 3 hr. with aniline (0·50 c.c.) in ethanol (5 c.c.). Recrystallisation of the product from ether gave *N*-phenyl-2 : 4 : 6-tri-*O*-methyl-D-glucosylamine (0·220 g.), m. p. 160—162°, $[\alpha]_D^{17}$ −113·5° (3·5 min.) ⟶ −79° (24 hr.) (*c*, 0·45 in dry MeOH) (Found: C, 60·8; H, 8·0; N, 4·9. Calc. for $C_{15}H_{23}O_5N$: C, 60·6; H, 7·8; N, 4·7%). Granichstädten and Percival (*loc. cit.*) recorded m. p. 162—166°,

$[\alpha]_D^{15}$ −113° (initially, in MeOH); Connell, Hirst, and Percival (*J.*, 1950, **3494**) gave m. p. 163—165°, $[\alpha]_D^{15}$ −81° (20 hr., in MeOH).

The residual syrupy aniline derivatives were treated for 2 hr. with 2N-sulphuric acid at 100° in a stream of carbon dioxide. The solution was neutralised with barium carbonate, filtered, and extracted with ether. The aqueous layer yielded a syrup (S), which was extracted with chloroform. The soluble portion, crystallised from ether, gave **2 : 3** : 6-tri-*O*-methyl-α-D-glucose (0·145 g.), m. p. and mixed m. p. 113—115°, $[\alpha]_D^{16}$ +69° (init.) ⟶ −33° (19 hr.) (*c*, 0·36 in methanolic 2% hydrogen chloride) (Found: C, 48·6; H, 8·3. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2%). Granichstädten and Percival (*loc. cit.*) recorded $[\alpha]_D^{18}$ +70° (init.) ⟶ −32° (24 hr.) (in methanolic 2% hydrogen chloride). A second sample (0·670 g.) of the syrup (S) was treated with *p*-phenylazobenzoyl chloride (2·20 g.) in pyridine (12 c.c.), and the products were fractionated on a column of alumina, as described by Coleman *et al.* (*loc. cit.*), to give **2 : 3 : 6**-tri-*O*-methyl-αβ-D-glucose **1** : 4-bis-*p*-phenylazobenzoate (0·295 g.), $[\alpha]_{6438}^{19}$ +5·7° (*c*, 0·60 in $CHCl_3$). Coleman *et al.* (*loc. cit.*) gave $[\alpha]_{6438}^{25}$ −1°, +1°, −5° (in $CHCl_3$) for samples prepared in this way.

(d) *Relative proportion of the tri-*O*-methylglucoses.* An unfractionated mixture of *O*-methylglucoses, prepared as above, showed $[\alpha]_D^{16}$ +70·8° (4 min.) ⟶ +22·6° (24 hr.) (*c*, 0·68 in methanolic 2% hydrogen chloride). The final value corresponded to that shown by a mixture of **2 : 3** : 6- and **2 : 4** : 6-tri-*O*-methyl-D-glucose containing 47% of the former ether (cf. Granichstädten and Percival, *loc. cit.*). [As a first approximation, the contribution of the small proportion (<1%) of the tetra-*O*-methyl-D-glucose in the hydrolysate can be neglected.]

*Periodate Oxidation of Sample* (B).—(a) *Periodate consumed.* A suspension of sample (B) (0·1132 g.) in 0·30M-sodium periodate (5·00 c.c.) was diluted to 250 c.c., and shaken at room temperature for several days, during which the polysaccharide gradually dissolved. Aliquot portions (25 c.c.) of the solution, and also of a blank from which the polysaccharide had been omitted, were removed at intervals, and analysed for periodate by Fleury and Lange's method (*J. Pharm. Chim.*, 1933, **17**, 107, 196). The periodate consumption, expressed in mols. per anhydroglucose unit, was: 0·26 (3·6 hr.), 0·36 (20 hr.), 0·38 (24 hr.), 0·40 (28 hr.), 0·47 (44 hr.), 0·48 (92 hr.).

(b) *Formic acid produced.* After 94 hr., a portion (50 c.c.) of the solution was treated with ethylene glycol (1 c.c.), and titrated to pH 6·6 (pH meter) against 0·01N-sodium hydroxide; the result indicated that the formic acid production was 0·030 mol. per anhydroglucose unit.

(c) *Hydrolysis of the oxidised polysaccharide.* After 94 hr., a portion (20 c.c.) of the solution containing the oxidised polysaccharide was dialysed, concentrated, and hydrolysed with 0·1N-sulphuric acid. The hydrolysate, freed from mineral matter, was examined on a paper chromatogram, and gave, *inter alia*, a spot having an $R_F$ value identical with that of glucose.

(d) *Treatment of the oxidised polysaccharide with phenylhydrazine.* A solution of sample (B) (0·100 g.) and 0·3M-sodium periodate (5·00 c.c.) in water (245 c.c.) was shaken at room temperature for 4 days, dialysed for 3 days, concentrated, and freeze-dried to a white solid (0·093 g.), which was then heated at 100° for 45 min. with a mixture (2·8 c.c.) of phenylhydrazine, acetic acid, and water (**2 : 2 : 5**, by vol.). The yellow precipitate dissolved when alcohol (15 c.c.) was added, indicating the probable absence of a polysaccharide osazone. Graded addition of water to the alcoholic solution gave glucosazone (0·020 g.), m. p. and mixed m. p. 203—204°.

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## 616. *Chemical Action of Ionising Radiations in Solution. Part XI.* The Action of Free Radicals, produced by X-Rays, on Lactic Acid in Aqueous Solution with Particular Reference to the Effect of Molecular Oxygen.*

By G. R. A. Johnson, G. Scholes, and J. Weiss.

The reactions of lactic acid in aqueous solution with the free radicals produced by the action of *X*-rays on the water have been investigated with particular attention to the processes occurring in the presence of molecular oxygen. Under these conditions, pyruvic acid is formed as the main product, together with hydrogen peroxide and some acetaldehyde.

A quantitative study under different experimental conditions has led to the formulation of a mechanism which accounts for all the main experimental results. The rôle of molecular oxygen is explained in terms of reactions involving (i) $HO_2$ radicals, formed by the addition of oxygen to the primarily formed H atoms, and (ii) organic peroxy-radicals of the type $HO_2C{\cdot}CMe(OH){\cdot}O_2{\cdot}$ produced by the addition of molecular oxygen to lactate radicals formed by a one-step dehydrogenation of lactic acid by OH radicals.

Earlier papers of this series (cf. Part X*) have reported reactions of free OH radicals in aqueous systems, the radicals being produced from the water by ionising radiations (*e.g.*, *X*-rays, $\gamma$-rays). From a biochemical point of view, reactions in the presence of molecular oxygen are of particular interest, since a marked effect of oxygen on the sensitivity of certain biological systems to ionising radiations has been observed by several workers.

We have previously reported that the presence of oxygen markedly increases the yields of pyruvic acid from α-alanine in aqueous solution (Johnson, Scholes, and Weiss, *Science*, 1951, **114**, 412). We have now studied the *X*-ray-induced oxidation of lactic acid in some detail. The only previous investigation of this system is that of Di Bella (*Boll. Soc. ital. Biol. sperim.*, 1949, **25**, 1268) who reported the formation of pyruvic acid which he identified by a colour reaction.

It is now well-established that the chemical effects of ionising radiations in dilute aqueous solutions are due to the free radicals produced by the splitting of the water molecules following absorption of the radiations, according to the net process (Weiss, *Nature*, 1944, **153**, 748; *Brit. J. Radiol.*, 1947, Suppl. **1**, 56) :

$$H_2O \longrightarrow\!\!\!\!\!\sim\!\!\!\!\!> H + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

More recently, it has been pointed out (cf. Allen, *Ann. Rev. Phys. Chem.*, 1952, **3**, 57) that a small part of the radiation energy absorbed by the water results in the direct formation of molecular hydrogen and hydrogen peroxide, which, according to Rigg and Weiss (cf. Weiss, *ibid.*, 1953, in the press), is due to the interaction of the primarily formed, excited, water molecules ($H_2O^*$) according to :

$$2H_2O^* \longrightarrow H_2 + H_2O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1b)$$

This " molecular " yield must also be taken into account in the interpretation of the experimental results.

In the results presented below, the yields are expressed in molar quantities; for convenience, therefore, the energy absorption is given in terms of ev/$N$ where $N = 6{\cdot}02 \times 10^{23}$. This is related to the Roentgen unit (r), which corresponds to an energy absorption of 83 ergs/g.) by the relation : $(ev/N)/g. = 1{\cdot}162 \times 10^{16}$ r. The " *G*-value " in radiation chemistry is defined as the number of molecules of products formed (or of substance decomposed) per 100 ev of energy absorbed. *G* for the formation of radicals, according to process (1*a*) is $G_R \simeq 4{\cdot}1$, and for the molecular yield of hydrogen peroxide and hydrogen according to reaction (1*b*) is $G_M \simeq 0{\cdot}7$ (cf. Weiss, *loc. cit.*, 1953).

When lactic acid is oxidised by free radicals produced by radiation, pyruvic acid and acetaldehyde are formed (they have been identified as 2 : 4-dinitrophenylhydrazones),

* Part X, *J.*, 1952, 3034.

together with hydrogen peroxide. Throughout the experiments 0·02M-aqueous lactic acid was used.

The dependence of the yield of pyruvic acid and hydrogen peroxide on total dose of radiation, at different pH values, in oxygen (1 atm.) saturated solutions, is shown in Figs. 1 and 2, the initial $G$-values being plotted in Fig. 3. Whereas the initial yield of hydrogen peroxide is independent of pH, that of pyruvic acid is independent only within the pH

FIG. 1. *Formation of pyruvic acid in the presence of oxygen* (1 *atm.*). *This and all other Figures refer to aqueous lactic acid* (0·02M), *irradiated with* X-*rays* (200 *kv*).

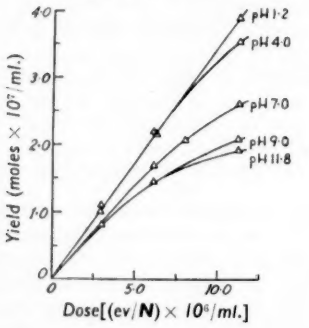
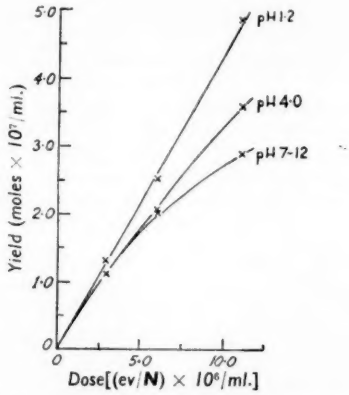



FIG. 2. *Formation of hydrogen peroxide in the presence of oxygen* (1 *atm.*).




ranges 1—4 and 7—12. The marked dependence of the yield on pH at higher doses, observed both for pyruvic acid and hydrogen peroxide formation, can be explained in terms of pH-dependent secondary processes discussed below, *i.e.*, processes involving competition between the primary reaction products and lactic acid for the free radicals. The dependence of the initial pyruvic acid yield on pH (Fig. 3) cannot however be explained in this way.

FIG. 3. pH-*Dependence of the initial* G-*values for the formation of pyruvic acid* (Δ) *and hydrogen peroxide* (×) *in the presence of oxygen.*

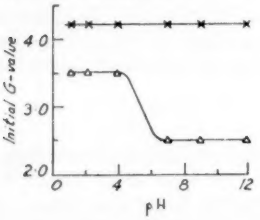
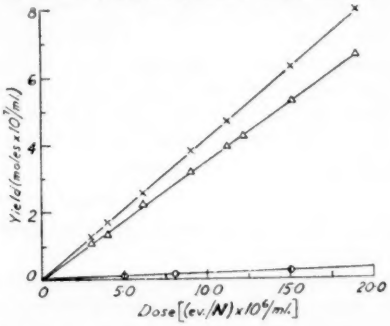



FIG. 4. *Formation of hydrogen peroxide* (×), *pyruvic acid* (Δ), *and acetaldehyde* (o) *in the presence of oxygen* (1 *atm.*), *at* pH *ca.* 1·2.




At pH 1·2 the yields of hydrogen peroxide and pyruvic acid are directly proportional to dose up to the highest doses used (Fig. 4); these conditions, therefore, are particularly suitable for studying the stoicheiometry of the primary reaction. From Fig. 4 it can be seen that the $G$-values for pyruvic acid and hydrogen peroxide formation are 3·5 and 4·2 respectively. The yield of hydrogen peroxide is, of course, made up of two parts: that produced in the actual oxidation process, and that produced directly from the water according to eqn. (1*b*). $G_{H_2O_2}$ of the oxidation reaction is, therefore, 3·5 ($= 4{\cdot}2 - 0{\cdot}7$), *i.e.*, equal to $G_{PA}$ (where the suffix PA refers to pyruvic acid).

Further information has been obtained by the irradiation of air-saturated solutions at pH 1·2 (Fig. 5). The rate of formation of hydrogen peroxide per unit dose changed sharply at a dose of $9 \times 10^{6}$ ev/**N**, presumably owing to exhaustion of the oxygen present in solution. The total amount of hydrogen peroxide present at the "break point" is $3{\cdot}6 \times 10^{-7}$ ($\pm 5\%$) mole/ml. The amount of hydrogen peroxide formed directly from water (eqn. 1*b*) after this dose is $0{\cdot}6 \times 10^{-7}$ mole/ml., so that the amount produced in the oxidation reaction is $3{\cdot}0 \times 10^{-7}$ mole/ml., *i.e.* it corresponds closely to the amount of oxygen in an air-saturated aqueous solution ($2{\cdot}9 \times 10^{-7}$ mole/ml.) Therefore, nearly all the oxygen originally present in solution can be converted into hydrogen peroxide. After the "break point," when no oxygen is present in the solution, the rate of formation of hydrogen peroxide corresponds to that produced by the molecular process (1*b*) ($G_{\mathrm{M}} \simeq 0{\cdot}7$).

Another point of interest arising from the air irradiations at pH 1·2, is that the rate of formation of pyruvic acid, within the range immediately before the oxygen is used up, exceeds the rate of formation in similar solutions saturated with oxygen (1 atm.) (Fig. 6).

In air-saturated solutions the maximum rate of formation of pyruvic acid corresponds to $G \simeq 8$.

From these results a mechanism can be derived for the reaction in acid solution.

FIG. 5. *Formation of hydrogen peroxide* (×), *pyruvic acid* (Δ), *and acetaldehyde* (o) *in the presence of air, at* pH *ca.* 1·2.

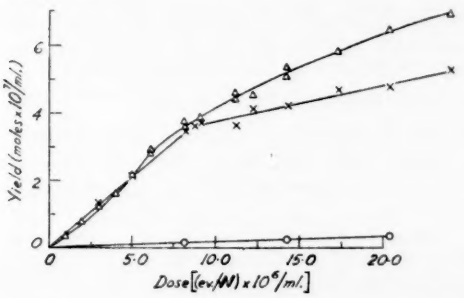
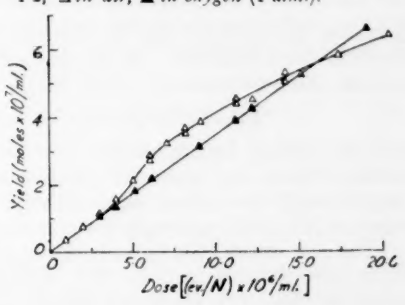



FIG. 6. *Formation of pyruvic acid at* pH *ca.* 1·2, Δ *in air,* ▲ *in oxygen* (1 *atm.*).




In general, the initial process in radiation-induced oxidations of organic compounds RH of this type may be assumed to be dehydrogenation by the hydroxyl radicals, produced according to eqn. (1*a*) :

$$\mathrm{RH} + \mathrm{OH} \longrightarrow \mathrm{R}\cdot + \mathrm{H_2O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The rôle of oxygen in enhancing the overall oxidation process can be ascribed to the following reactions : (*a*) Reaction of the H atoms produced in (1*a*), according to :

$$\mathrm{H} + \mathrm{O_2} \longrightarrow \mathrm{HO_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

This process can effectively inhibit the back-reactions :

$$\mathrm{H} + \mathrm{OH} \longrightarrow \mathrm{H_2O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\mathrm{R}\cdot + \mathrm{H} \longrightarrow \mathrm{RH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

(*b*) Direct addition of molecular oxygen to the organic radicals initially formed :

$$\mathrm{R}\cdot + \mathrm{O_2} \longrightarrow \mathrm{RO_2}\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

In the particular case of lactic acid oxidation, the results can be accounted for on the basis of the following reactions :

$$\mathrm{CHMe(OH)\cdot CO_2H} + \mathrm{OH} \longrightarrow \cdot\mathrm{CMe(OH)\cdot CO_2H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$\cdot\mathrm{CMe(OH)\cdot CO_2H} + \mathrm{O_2} \longrightarrow \cdot\mathrm{O_2\cdot CMe(OH)\cdot CO_2H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$\cdot\mathrm{O_2\cdot CMe(OH)\cdot CO_2H} + \mathrm{HO_2} \longrightarrow \mathrm{Me\cdot CO\cdot CO_2H} + \mathrm{H_2O_2} + \mathrm{O_2} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Reaction (9) can be regarded as a simple electron transfer from the organic peroxy-radical to the $HO_2$ radical, followed by the loss of a proton and an $O_2$ molecule according to :

$$\cdot O_2\cdot CMe(OH)\cdot CO_2H + HO_2 \longrightarrow \cdot O_2\cdot CMe(OH)\cdot CO_2H\}^+ + HO_2^- \quad . \quad . \quad . \quad (9a)$$

$$\cdot O_2\cdot CMe(OH)\cdot CO_2H\}^+ + HO_2^- \longrightarrow \cdot O_2\cdot CMe(:O)\cdot CO_2H + H_2O_2 \quad . \quad . \quad . \quad . \quad (9b)$$

$$\cdot O_2\cdot CMe(:O)\cdot CO_2H \longrightarrow Me\cdot CO\cdot CO_2H + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9c)$$

A possible alternative mechanism involves decomposition of the peroxy-radical according to :

$$\cdot O_2\cdot CMe(OH)\cdot CO_2H \longrightarrow Me\cdot CO\cdot CO_2H + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

followed by the interaction of the $HO_2$ radicals to form hydrogen peroxide :

$$2HO_2 \longrightarrow H_2O_2 + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Reactions (10) and (11) would also account for the above results in acid solutions.

These two schemes would explain (i) the observed $G$-values for pyruvic acid and hydrogen peroxide formation, (ii) the equal yields of pyruvic acid and hydrogen peroxide, and (iii) the fact that all the molecular oxygen present in solution can be converted into hydrogen peroxide.

Another possible reaction of the organic peroxy-radicals is a dismutation; the results could be explained if this occurred thus :

$$2\cdot O_2\cdot CMe(OH)\cdot CO_2H \longrightarrow 2Me\cdot CO\cdot CO_2H + H_2O_2 + O_2 \quad . \quad . \quad . \quad . \quad . \quad (12)$$

However, it is unlikely that interaction of the organic peroxy-radicals, if it occurred, would result in these products. A simple electron transfer between two of the organic peroxy-radicals should ultimately lead to the products as indicated by the following reaction :

$$2\cdot O_2\cdot CMe(OH)\cdot CO_2H \longrightarrow Me\cdot CO\cdot CO_2H + HO_2\cdot CMe(OH)\cdot CO_2H + O_2 \quad . \quad . \quad . \quad (13)$$

and the organic hydroperoxide thus formed would probably decompose to acetic acid, carbon dioxide, and water (cf. Bunton *et al.*, *Nature*, 1949, **163**, 444). Since, in this case, oxygen would be utilised without the production of hydrogen peroxide, a process such as reaction (13) could not explain our results.

The rôle of the $HO_2$ radicals in this system must be as outlined above, *i.e.*, either they react with the intermediate $RO_2$ radicals (eqn. 9) or they recombine to form hydrogen peroxide (eqn. 11), since the dehydrogenation of lactic acid according to the reaction $RH + HO_2 \longrightarrow R\cdot + H_2O_2$ would be incompatible with the observed stoicheiometry.

Formation of radicals of the type $RO_2$ has previously been assumed by Kolthoff and Medalia (*J. Amer. Chem. Soc.*, 1949, **71**, 3777) to account for the influence of oxygen in the action of Fenton's reagent on various organic compounds, and also by Dewhurst (*Trans. Faraday Soc.*, 1952, **48**, 905) to explain the yields of ferric salt produced on irradiation of aerated aqueous-alcoholic ferrous sulphate solutions with $\gamma$-rays. Similarly, we have observed that the presence of $Fe^{2+}$ ions during the irradiation of aerated lactic acid solutions greatly increases the yields of pyruvic acid. For example, from 0·02M-lactic acid containing 0·001M-ferrous sulphate (pH $\sim$ 1·0) pyruvic acid was produced in yields corresponding to $G = 90$ at a total dose of about $2 \times 10^{-7}$ (ev/$N$)/ml. No comparable increase in the pyruvate yields was observed if lactic acid–ferrous sulphate solutions of similar concentrations were irradiated *in vacuo*. These results can be explained by a chain mechanism involving $Fe^{2+}$ and $RO_2$ radicals, which will be dealt with in a later publication.

Another interesting feature is the relatively high $G$-value (*ca.* 8) for pyruvic acid formation attained in the irradiation of air-saturated solutions just before exhaustion of the dissolved oxygen (Fig. 5). Here it is reasonable to suppose that there is insufficient oxygen present to react with all the lactate radicals produced according to eqn. (7), so that organic peroxy-radicals may react with lactate radicals, *e.g.*, as follows :

$$\cdot O_2\cdot CMe(OH)\cdot CO_2H + \cdot CMe(OH)\cdot CO_2H \longrightarrow 2\cdot O\cdot CMe(OH)\cdot CO_2H \quad . \quad . \quad . \quad . \quad (14)$$

If the species produced in reaction (14) were capable of dehydrogenating lactic acid according to reaction (15), then the sequence (14), (15), (16) could lead to an increased yield of pyruvic acid as long as any oxygen is present in the solution. The relatively high $G_{PA}$

(*ca.* 8) in aerated solutions can only be explained on the basis of a process involving short chains such as that outlined above. Reactions (14), (15), and (16) would not alter the rate of hydrogen peroxide formation, and in fact, this remains linear with dose up to the point where the oxygen is completely exhausted (cf. Fig. 5). The amount of oxygen "lost" (*i.e.*, not converted into hydrogen peroxide) by reactions (14) and (15) is, at most, $0{\cdot}35 \times 10^{-7}$ mole; this is within the experimental error of determination of the "break" in the hydrogen peroxide yield–dose curve (Fig. 5).

In considering the reaction mechanism in solutions of pH >4 we are confronted with two new factors: a change in the initial *G*-value for pyruvate formation from 3·5 (in acid solution) to 2·5 (Fig. 3); and the occurrence of marked secondary reactions, involving the (accumulated) primary products (cf. Figs. 1 and 2).

There is no evidence to suggest that the primary effect of the ionising radiation on water changes over the pH range considered here. Furthermore, in view of the constancy of the initial $G_{H_2O_2}$, it appears that the ratio of the number of free radicals attacking lactic acid to the number of free radicals lost in other ways (*e.g.*, by recombination) remains constant over the whole pH range. The observed initial *G*-values can, however, be explained tentatively in terms of the stability of the organic peroxy-radical. At pH >4 this species might exist predominantly in the anionic form $\cdot O_2 \cdot CMe(OH) \cdot CO_2^-$. Since the hydroperoxy-radical ($HO_2$) would exist here largely as the anion $O_2^-$, reaction (9) might be inhibited by electrostatic forces. For the same reason, any dismutation reaction between these anionic organic peroxy-radicals could be minimised. As these radicals might be expected to have only a limited life they may undergo spontaneous decarboxylation, so that the reactions (17) and (18), or (19) may occur

$$\cdot O \cdot CMe(OH) \cdot CO_2H + CHMe(OH) \cdot CO_2H \longrightarrow Me \cdot CO \cdot CO_2H + \cdot CMe(OH) \cdot CO_2H + H_2O \quad (15)$$

$$\cdot CMe(OH) \cdot CO_2H + HO_2 \longrightarrow Me \cdot CO \cdot CO_2H + H_2O_2 \quad (16)$$

$$\cdot O_2 \cdot CMe(OH) \cdot CO_2^- \longrightarrow {}^-O_2 \cdot CMe(OH) \cdot + CO_2 \quad (17)$$

$$HO_2 \cdot CMe(OH) \cdot + O_2^- \longrightarrow {}^-O_2 \cdot CHMe \cdot OH + O_2 \quad (18)$$

$$\cdot O_2 \cdot CHMe \cdot OH + \cdot O_2 \cdot CMe(OH) \cdot CO_2^- \longrightarrow HO_2 \cdot CHMe \cdot OH + Me \cdot CO \cdot CO_2^- + O_2 \quad (19)$$

These reactions would thus lower the initial yield of pyruvic acid. The apparent yield of peroxide might not be altered, however, since the 1-hydroxyethyl hydroperoxide (Rieche, *Ber.*, 1931, **64**, 2378) formed in reaction (19) should behave similarly to hydrogen peroxide in the reaction used for determination of the latter (see Experimental section).

The above explanation of the effect of pH on the initial *G*-values is necessarily tentative; it does, however, account for the production of acetaldehyde and qualitatively also for the pH-dependence of the yield of this substance (cf. Figs. 4 and 7), since the aldehyde could arise from a dismutation process, *viz.*:

$$2 \cdot O_2 \cdot CHMe \cdot OH \longrightarrow HO_2 \cdot CHMe \cdot OH + Me \cdot CHO + O_2 \quad (20)$$

The explanation of the non-linearity of the yield–dose curves for pyruvic acid and hydrogen peroxide in neutral and alkaline solutions (Figs. 1 and 2) cannot be attributed solely to an oxidation of pyruvic acid by hydrogen peroxide, produced during the irradiation. Although this oxidation is known to take place in neutral and alkaline solution (cf. Everett and Sheppard, *Univ. Oklahoma Med. School, Dept. Biochem.*, 1944), it can be shown that it is insufficient to account for the shape of the curves in Figs. 1 and 2. For instance, in solutions containing $2 \times 10^{-4}$M-pyruvic acid and $2 \times 10^{-4}$M-hydrogen peroxide at pH 7, the loss of pyruvic acid and hydrogen peroxide was found to be less that $10^{-7}$ mole/min. The alternative explanation is that pyruvic acid and/or hydrogen peroxide, when formed in sufficient amounts, can compete with lactic acid for the primary radicals. That such secondary processes do, in fact, take place, has been shown by experiments in which pyruvic acid or hydrogen peroxide was added to lactate solutions before irradiation; the addition of either of these substances in concentrations of about $10^{-4}$M can effect a marked lowering of the oxidation yields.

Secondary processes might be expected since it is well-known that the $HO_2$ radical is ionised ($HO_2 \rightleftarrows H^+ + O_2^-$), and as the hydrogen peroxide and pyruvate concentrations

increase, reactions (21) and (22) could become significant. Reaction (21) would lower the yield of hydrogen peroxide but not necessarily that of pyruvic acid, as here a further OH radical is generated. Reaction (22) would lower the yields of both hydrogen peroxide and pyruvic acid. The experimental results can be accounted for qualitatively by a pH-dependent competition of hydrogen peroxide and pyruvic acid for $O_2^-$.

$$O_2^- + H_2O_2 \longrightarrow O_2 + OH^- + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

$$O_2^- + Me{\cdot}CO{\cdot}CO_2H \longrightarrow {\cdot}O_2{\cdot}CMe(OH){\cdot}CO_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)$$

A further feature of the results obtained on irradiation of aerated solutions is the rate of formation of pyruvic acid after the oxygen initially present in the solution has been used up, which exceeds that observed in evacuated solutions (cf. Figs. 5, 7, and 8). This effect can be attributed, in part, to the hydrogen peroxide present in the solution, since

FIG. 7. *Formation of hydrogen peroxide* (×), *pyruvic acid* (Δ), *and acetaldehyde* (○) *in the presence of air at* pH *ca.* 7·0.

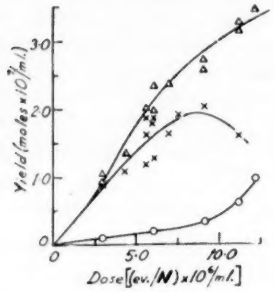
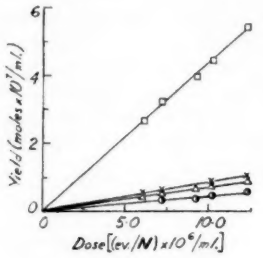



FIG. 8. *Formation of hydrogen* (□), *hydrogen peroxide* (×), *pyruvic acid* (Δ), *and carbon dioxide* (◑) in vacuo *at* pH *ca.* 1·2.



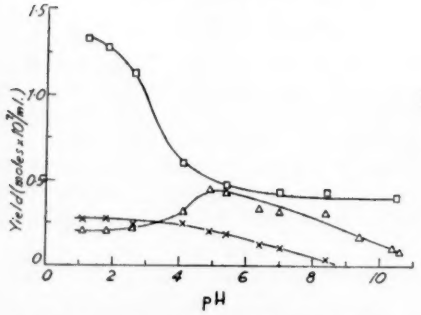




FIG. 9. pH-*Dependence of the formation of hydrogen* (□), *pyruvic acid* (Δ), *and hydrogen peroxide* (×), in vacuo. *Dose* = $3{\cdot}0 \times 10^{-6}$ (ev/N)/*ml.*

addition of hydrogen peroxide to evacuated lactic acid solutions before irradiation increased the yields of pyruvic acid. At pH 1·2, however, hydrogen peroxide does not apparently undergo any net decomposition (cf. Fig. 5).

The explanation of this effect in acid solution is not quite clear. Since, however, it has been suggested (Weiss, *Nature*, 1950, **167**, 728) that an equilibrium exists between hydrogen atoms and hydrogen ions :

$$H + H^+ \rightleftharpoons H_2^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (23)$$

a possible rôle of hydrogen peroxide may, in this case, involve reaction (24*a*) or (24*b*), followed by (25). Although, on general kinetic grounds, reaction (24*a*) is perhaps more likely than (24*b*), it is doubtful whether the former can play any significant part in acid solution, where the concentration of $HO_2^-$ is very small. However, too little is known at

$$H_2^+ + HO_2^- \longrightarrow H_2 + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24a)$$

$$H_2^+ + H_2O_2 \longrightarrow H_2 + HO_2 + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24b)$$

$${\cdot}CMe(OH){\cdot}CO_2H + HO_2 \longrightarrow Me{\cdot}CO{\cdot}CO_2H + H\,O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (25)$$

present about the relevant rate constants and about the local concentrations of H atoms and other radicals produced by the radiation to make decision possible. On the other hand, our experiments seem to indicate that a chain reaction between the organic radical $\cdot CMe(OH)\cdot CO_2H$ and hydrogen peroxide, as suggested by Waters (" The Chemistry of Free Radicals," Oxford, 1949, p. 251), does not take place under these conditions.

At pH 7 the results are somewhat irreproducible, but it has been established that the yield of hydrogen peroxide falls after exhaustion of molecular oxygen (Fig. 7). This can be attributed to the decomposition reaction :

$$H + H_2O_2 \longrightarrow H_2O + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (26)$$

which produces another OH radical and so increases the yield of pyruvic acid. The observed increase in the yield of acetaldehyde after exhaustion of oxygen could, perhaps, be accounted for by the reactions :

$$HO_2\cdot CHMe\cdot OH + H \longrightarrow \cdot O\cdot CHMe\cdot OH + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (27)$$

$$\cdot O\cdot CHMe\cdot OH + CHMe(OH)\cdot CO_2H \longrightarrow Me\cdot CHO + \cdot CMe(OH)\cdot CO_2H + H_2O \quad . \quad . \quad (28)$$

The mechanism of the effects of *X*-rays on lactic acid in evacuated solutions presents a somewhat complex picture, particularly with regard to the pH-dependence of the yields. An unusual feature is the rather high yield of molecular hydrogen in acid solution, which decreases rapidly with increasing pH. Again, the initial yield appears to depend on pH. It should be noted also that even the hydrogen peroxide produced by the molecular reaction (1*b*) is rapidly decomposed in non-acid solutions (Fig. 9).

The results obtained *in vacuo* can be explained tentatively by the following reaction mechanism [R = $CMe(OH)\cdot CO_2H$] :

$$RH + OH \longrightarrow R\cdot + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$R\cdot + RH \longrightarrow R_2 + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (29)$$

$$2R\cdot \longrightarrow Me\cdot CO\cdot CO_2H + RH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (30)$$

$$H + H^+ \rightleftarrows H_2^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (23)$$

$$H + H_2^+ \longrightarrow H_2 + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (25)$$

$$R\cdot + H \longrightarrow RH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In strongly acid solutions, it appears that most of the R radicals react with lactic acid [reaction (29)] since the *G*-value for hydrogen is quite high (4·4). Pyruvic acid is formed by the dismutation process (30).

When the pH is increased the concentration of $H_2^+$ decreases, thus leading to an increase in the back-reaction (5). At the same time, increased ionisation of the lactic acid may inhibit the reaction (29), thus leading to an increase in the disproportionation reaction and to a greater yield of pyruvic acid. This in turn (at pH 3—5) (Fig. 9) may be associated with an increase in the number of OH radicals from the decomposition of hydrogen peroxide by hydrogen atoms according to reaction (26). At high pH's, the yield of pyruvic acid is not fully reproducible, although there appears to be a net decomposition of this substance, probably of a reductive nature. Complete analysis of the mechanism in evacuated solutions has not yet been achieved.

The addition of oxygen to an organic radical, as postulated above, may be of importance in certain other radiation-induced oxidations, as, for example, in the formation of acetaldehyde from ethanol and from ethylamine, the formation of oxaloacetic acid from malic acid, and of α-keto-acids from α-amino-acids where it has been observed (Johnson, Scholes, and Weiss, unpublished experiments) that, as with lactic acid, oxygen enhances the yields very considerably.

It has been reported that oxygen has a marked effect on the sensitivity of certain biological systems to ionising radiations; decrease in oxygen tension during irradiation has been found to decrease the frequency of lethal mutations and chromasomal abberations (cf. Giles, Symposium on Radiobiology, New York, 1952, p. 257; Anderson, *Proc. Nat. Acad. Sci.*, 1951, **37**, 340), and to decrease the inactivation rate and duration of mitotic

inhibition (Hollaender, Stapleton, and Martin, *Nature*, 1950, **167**, 103; Gaulden and Nix, *Genetics*, 1950, **35**, 665). In view of our results, it is apparent that such enhancing effects of oxygen *in vivo* should not be attributed simply to $HO_2$ radicals and/or hydrogen peroxide, but also to the formation of peroxy-radicals of the type $RO_2$, *i.e.*, to the addition of oxygen to a primarily formed organic free radical. Although in oxygen-saturated solutions we have not observed any chain reactions in the system studied, it is conceivable that some $RO_2$ radicals, produced from cellular components, may undergo chain reactions and thus lead to a marked enhancement of the effects of the radiation.

Finally, the fact that pyruvate can compete very successfully for the free radicals produced by the radiation, even in the presence of relatively large concentrations of lactate, indicates that pyruvate is a very efficient radical-acceptor. This may be of some significance in view of the finding (Thomson, Mefford, and Wyss, *J. Bact.*, 1951, **62**, 39) that pyruvate can protect bacterial suspensions against the lethal and mutagenic action of *X*-rays.

## Experimental

*Irradiations.*—The solutions (150 ml.) were irradiated with *X*-rays generated from a Victor Maximar therapy tube operating at 200 kv and 15 ma, the irradiation arrangements being similar to those described in Part I (Farmer, Stein, and Weiss, *J.*, 1949, 3241). The dose rate was determined by measuring the oxidation of 0·001M-ferrous sulphate in 0·1N-sulphuric acid and was $2 \times 10^{-7}$ (ev/***N***) per ml. per min., $G_{Fe^{3+}}$ being assumed to be 18 (Rigg and Weiss, in the press).

The lactic acid solutions were prepared in triply distilled water, ordinary distilled water being redistilled in an all-glass still from alkaline permanganate and then from phosphoric acid. Where necessary, the solutions were buffered by the following systems: for pH<4, $H_2SO_4$; pH 5—8, $KH_2PO_4$—$Na_2HPO_4$ (Sørensen); pH 8—10, $Na_2B_4O_7$—$Na_2CO_3$ (Parnas); for pH>10, NaOH.

Irradiations were carried out in the presence of air or of oxygen (the solutions being saturated by passage of oxygen for *ca.* 20 min.), and also after evacuation as follows: The solution was pumped out by means of a Hyvac oil pump, shaken for a few minutes, and finally evacuated with a mercury diffusion pump. After this procedure less than 0·01 ml. of non-condensable gas remained.

All materials used were of "AnalaR" grade. The lactic acid contained not more than 15% of anhydrides as measured by the method of Fetzer and Jones (*Analyt. Chem.*, 1952, **24**, 835). The presence of these amounts of anhydrides during irradiation had no effect on the yields; identical results were obtained when the lactic acid solutions contained anhydrides and when the anhydrides were removed by the hydrolysis procedure of Dietzel and Krug (*Ber.*, 1925, **58**, 1307).

*Identification of Pyruvic Acid.*—The irradiated solution was treated with 0·25% solution of 2 : 4-dinitrophenylhydrazine in 30% perchloric acid, and after 30 min. extracted twice with chloroform. The hydrazone was removed from the chloroform by extraction with 10% aqueous sodium carbonate. Pyruvic acid 2 : 4-dinitrophenylhydrazone, precipitated on acidification of the carbonate extract with concentrated hydrochloric acid and recrystallised from ethanol, had m. p. and mixed m. p. 212—214°.

*Identification of Acetaldehyde.*—The irradiated solution was treated with 2 : 4-dinitrophenylhydrazine solution, as described above, and after 30 min. extracted with carbon tetrachloride. The organic layer was washed with 10% aqueous sodium carbonate, and twice with 30% perchloric acid to remove excess of the hydrazine reagent, and evaporated to dryness *in vacuo*. The residue was taken up in light petroleum (b. p. 80—100°; 1 ml.). The presence of acetaldehyde 2 : 4-dinitrophenylhydrazone in this residue was established by paper chromatography with light petroleum–methanol as solvent (Meigh, *Nature*, 1952, **170**, 579).

*Quantitative Methods.*—To avoid possible interaction between hydrogen peroxide and pyruvic acid formed in the solution, analyses were carried out immediately after irradiation.

(a) *Hydrogen peroxide.* An aliquot of the irradiated solution was treated with titanium sulphate reagent (5 ml.) (Eisenberg, *Ind. Eng. Chem., Anal. Edn.*, 1943, **15**, 327), then made up to 50 ml., and the extinction was measured on a "Spekker" photoelectric absorptiometer with an Ilford 601 filter.

(b) *Pyruvic acid.* Friedman and Haugen's method (*J. Biol. Chem.*, 1943, **147**, 415), which involves the determination of pyruvic acid as its 2 : 4-dinitrophenylhydrazone, was modified to

permit the use of larger samples and lower pyruvate concentrations. To an aliquot (1—20 ml.) of the test solution in a separating funnel 5 ml. of a 0·25% solution of 2 : 4-dinitrophenylhydrazine in 30% perchloric acid were added. After 15 min. at room temperature the mixture was extracted with chloroform (2 × 20 ml.). The extracts were extracted with 10% aqueous sodium carbonate (10 ml.), and the aqueous layer was washed into a 50-ml. flask with a further 10 ml. of 10% sodium carbonate solution. 2N-Sodium hydroxide (5 ml.) was added, and the whole then diluted to 50 ml. After a few minutes the extinction of the final cherry-red solution was measured, with an Ilford 603 filter. For each estimation a blank test was carried out.

Calibration was with pyruvic acid (three times distilled *in vacuo*) and with pyruvic acid 2 : 4-dinitrophenylhydrazone (m. p. 212—214°), which gave identical results.

The method gave good recoveries of pyruvic acid from lactic acid solutions under the conditions used in the irradiation experiments and was accurate to ±3% with pyruvate concentration of not less than $5 \times 10^{-6}$M.

(c) *Acetaldehyde.* An aliquot of the test solution (5—25 ml.) was diluted to 25 ml. and to it was added a solution (5 ml.) containing 0·25% of 2 : 4-dinitrophenylhydrazine in 30% perchloric acid. After 30 min. at room temperature the mixture was extracted with carbon tetrachloride (20 ml.) for exactly 1 min. and then again with carbon tetrachloride (5 ml.) for 30 sec. Pyruvic acid 2 : 4-dinitrophenylhydrazone was removed by shaking the combined carbon tetrachloride extracts with 10% aqueous sodium carbonate (10 ml.) for 30 sec. The carbon tetrachloride layer was made up to 50 ml. with ethanol, and the final solution treated with 2 ml. of ethanolic 0·1N-sodium hydroxide. After exactly 5 min. the intensity of the red colour was determined with an Ilford 603 filter. Blank determinations were carried out. Calibration was by acetaldehyde (purified through the ammonia derivative; cf. Snell, "Colorimetric Methods of Analysis," New York, 1937, Vol. II, p. 64) and its 2 : 4-dinitrophenylhydrazone (m. p. 161—163°), which gave identical results.

The method was reproducible within ± 3% with aldehyde concentrations down to $5 \times 10^{-6}$M.

(d) *Gas analysis.* The apparatus was similar to that described by Stein and Weiss (*J.*, 1949, 3245). After irradiations *in vacuo*, the gases were pumped from the vessel through a liquid air trap by means of a semi-automatic Töpler pump. The hydrogen was determined manometrically after combustion in the presence of excess of oxygen. Carbon dioxide which was condensed in the liquid-air trap was determined manometrically after fractional distillation from freezing acetone (Baldwin, *J.*, 1949, 720).

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## 617. *The Chemistry of Fluorene. Part III.* The Condensation of 9-Fluorenylsodium with Acid Chlorides and Anhydrides.*

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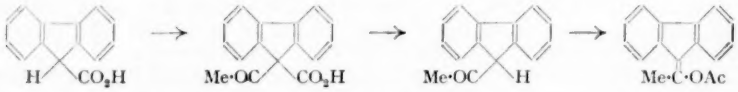
9-Fluorenylsodium with lower acyl halides and anhydrides yields 9-1′-acyloxyalkylidenefluorenes, unlike 9-fluorenyl-lithium which gives 9 : 9-diacylfluorenes. Phthalic anhydride or phthaloyl chloride yields fluorenylidenephthalide and 2 : 5-difluorenylidene-2 : 5-dihydro-3 : 4-benzofuran, and succinic anhydride yields the corresponding compounds. Naphthalic anhydride and 9-fluorenylsodium give the mono-9-fluorenylidene analogue and fluorene-9′-*spiro*-2-perinaphthane-1 : 3-dione.

In Part I (*J.*, 1951, 2848) the production of 9-alkyl derivatives of fluorene by the condensation of 9-fluorenylsodium with alkyl halides was described. This condensation has now been extended to some acid chlorides and anhydrides.

The reaction of acetyl chloride or acetic anhydride with 9-fluorenylsodium yields, as the main product, 9-1′-acetoxyethylidenefluorene (I), identified by its preparation by the acetylation of 9-acetylfluorene (Von and Wagner, *J. Org. Chem.*, 1944, **9**, 155), by formation of a dibromide and a picrate, and by its ultra-violet spectrum which showed it to have a

* Part II, *J.*, 1952, 986.

dibenzofulvene structure. It was identical with the compound prepared by Stollé and Ester (*J. pr. Chem.*, 1931, **132**, 14) from diphenyleneacetic acid, acetic anhydride, and sodium acetate and described by them as 9 : 9-diacetylfluorene. The following mechanism leading to (I) appears more probable than that put forward by these authors, and it is supported by the fact that 9-methylfluorene-9-carboxylic acid yields 9-methylfluorene as the sole product under their conditions.



(I)

The yields of (I) obtained from the chloride or anhydride were, at best, only about 33%. Condensation of trifluoroacetic anhydride with 9-fluorenylsodium gave 9-trifluoroacetylfluorene in low yield. The product in this case was not a dibenzofulvene derivative, presumably because the strong intermolecular hydrogen bonding between the 9-hydrogen atom of one molecule and the trifluoroacetyl group in another, which is indicated by the high molecular weight and high melting point, prevented enolisation.

Condensation of 9-fluorenyl-lithium with an acid chloride appears to yield the 9 : 9-diacyl derivative rather than a dibenzofulvene derivative (Kliegl, Weng, and Wiest, *Ber.*, 1930, **63**, 1262), and it therefore seemed probable that the so-called 9-acetylfluorene prepared by Miller and Bachman (*J. Amer. Chem. Soc.*, 1935, **57**, 766) is, in fact, 9 : 9-diacetylfluorene. Their structure is based on analysis of an oxime, m. p. 167°, which could quite readily be formed from the diacetyl compound by simultaneous hydrolysis of one acetyl group (cf. Kliegl *et al.*, *loc. cit.*). We found that both 9-acetylfluorene (m. p. 75—77°) and 9-1′-acetoxyethylidenefluorene yield 9-acetylfluorene oxime, m. p. 167°, which may be a stereoisomer of the oxime melting at 137° described by Von and Wagner (*loc. cit.*). On storage at 0° 9-acetylfluorene is converted into a crystalline hydroperoxide.

It might be expected that 9-methyl-9-fluorenylsodium would condense with acid chlorides or anhydrides to give good yields of 9-acyl-9-methylfluorenes. With acetyl chloride or acetic anhydride, however, an almost quantitative yield of 9-methylfluorene with a small amount of 9 : 9′-dimethyldi-9-fluorenyl was obtained.

Propionyl chloride condensed with 9-fluorenylsodium yielded 9-1′-propionoxypropylidenefluorene, analogous to (I). This compound has a typical dibenzofulvene ultra-violet spectrum and readily forms a picrate. 9-Mono- or 9 : 9-di-substituted fluorenes do not in general form molecular complexes with picric acid.

9-1′-Acetoxyethylidene- and 9-1′-propionoxypropylidene-fluorene formed dibromides which readily lost hydrogen bromide to yield monobromo-compounds whose ultra-violet spectra are similar to that of 9-bromofluorene.

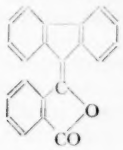
With carbonyl chloride, 9-fluorenylsodium yielded an oil from which, after treatment with methanol, unchanged fluorene, di-9-fluorenyl ketone, and methyl fluorene-9-carboxylate were isolated. Under somewhat different conditions, di-9-fluorenyl-9-carboxylic acid was also isolated, its identity being proved by synthesis from difluorenyl by reaction with sodamide and subsequent carboxylation.

Dibasic acid chlorides or anhydrides yielded more complex products with 9-fluorenylsodium. Phthaloyl chloride or phthalic anhydride gave as a main product a yellow compound $C_{21}H_{12}O_2$, which forms a dibromide (whose ultra-violet spectrum is of the 9-bromofluorene type) and on hydrolysis yields a colourless acid. This product is therefore 3-9′-fluorenylidenephthalide (II) (Wislicenus and Neber, *Annalen*, 1919, **418**, 274). A second product of this reaction is a crystalline solid with a greenish metallic lustre which yields intensely red solutions. Its analysis and its ready formation of a colourless tetrabromide lead us to regard it as 2 : 5-di-9′-fluorenylidene-2 : 5-dihydro-3 : 4-benzofuran (III).

Succinic anhydride yields the corresponding γ-9-fluorenylidenebutyrolactone and 2 : 5-di-9′-fluorenylidenetetrahydrofuran. Naphthalic anhydride on the other hand gave in addition to (IV), which is analogous to (II), a product $C_{25}H_{14}O_2$ which forms a dioxime and whose infra-red spectrum indicates the presence of a ketone group. On treatment with phenylhydrazine it yields fluorene and *N*′-phenyl-*NN*-naphthalohydrazide. It is therefore fluor-

ene-9′-*spiro*-2-perinaphthane-1 : 3-dione (V). After all condensations of dibasic acids or anhydrides with 9-fluorenylsodium bisdiphenylene-ethylene and/or difluorenyl were found among the products.

2 : 5-Di-9′-fluorenylidenetetrahydrofuran added bromine readily, to yield a colourless product which however on attempted purification evolved hydrogen bromide and bromine,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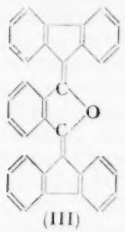
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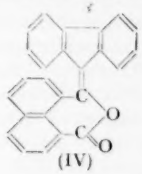
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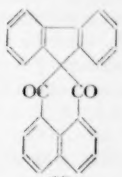
(V)

to yield a bronze-green product, $C_{30}H_{18}O$, which is probably 2 : 5-difluorenylidene-2 : 5-dihydrofuran. It was hoped that this compound could be prepared by condensation of maleic anhydride with 9-fluorenylsodium but this gave a complex mixture, of which bisdiphenylene-ethylene was the only coloured ingredient.

## Experimental

Silica gel used for chromatography was 100—120 mesh, 100 c.c. of gel being used for the treatment of 3·5 g. of material. Elution was carried out with, successively, light petroleum (b. p. 60—80°), benzene, chloroform, and chloroform–ethanol.

Bromides were prepared by adding to the unsaturated compound (0·5 g.) in carbon tetrachloride (20—80 c.c.) the theoretical amount of bromine as a 1% v/v solution in carbon tetrachloride. The mixture was stored overnight at 0° and was evaporated at about 40° under reduced pressure. The residue was crystallised from ethanol or light petroleum.

9-1′-*Acetoxyethylidenefluorene.*—(*a*) To 9-fluorenylsodium (from 100 g. of fluorene) (*J.*, 1951, 2848) suspended in light petroleum (b. p. 60—80°) (300 c.c.), acetyl chloride (100 c.c.) in light petroleum (b. p. 60—80°) (100 c.c.) was added slowly, with shaking, and the mixture stored overnight, evaporated, and extracted with ether. The extract on evaporation left a residue which on crystallisation gave fluorene (63 g.). The mother-liquor after evaporation and crystallisation of the residue from methanol gave a solid (10 g.), m. p. 74—75°. This gave a *picrate* (in acetic acid), m. p. 128° (Found: C, 57·2; H, 3·7; N, 8·6. $C_{23}H_{17}O_9N_3$ requires C, 57·6; H, 3·6; N, 8·8%), which on decomposition gave pale yellow 9-1′-*acetoxyethylidenefluorene* (5 g.), m. p. 97—98° (needles from light petroleum) (Found: C, 81·85; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

With 1 mol. of bromine 9-1′-acetoxyethylidenefluorene (0·5 g.) gave a mixture containing 9-(1-*acetoxy*-1-*bromoethyl*)-9-*bromofluorene* (0·4 g.), m. p. 91° (needles from light petroleum, b. p. 60—80°) (Found: C, 49·3; H, 3·3; Br, 39·7. $C_{17}H_{14}O_2Br_2$ requires C, 49·7; H, 3·4; Br, 39·2%), and 9-1′-*acetoxyvinyl*-9-*bromofluorene* (0·1 g.), m. p. 109—110° (needles from light petroleum, b. p. 60—80°) (Found: C, 62·3; H, 4·0; Br, 24·8. $C_{17}H_{13}O_2Br$ requires C, 62·0; H, 3·95; Br, 24·3%).

The structures of these three compounds were confirmed by resemblance of their ultraviolet spectra with those of 9-ethylidene- (see Table) and 9-bromo-fluorene.

(*b*) 9-Fluorenylsodium (from 40 g. of fluorene) was suspended in light petroleum (b. p. 100—120°) (250 c.c.), and acetic anhydride (60 c.c.) added with shaking. The mixture was heated under reflux for 3 hr. and the sodium acetate filtered off. Evaporation and crystallisation from methanol gave fluorene (11·6 g.) and 9-1′-acetoxyethylidenefluorene, m. p. 98—99° (15·9 g.). The methanol filtrates with picric acid afforded 9-1′-acetoxyethylidenefluorene picrate (10·1 g.), which on decomposition gave a further 4·0 g. of product.

(*c*) 9-Acetylfluorene (3 g.), acetic anhydride (8 c.c.), and pyridine (15 c.c.) were heated under reflux for 4 hr. and the cooled mixture poured into water. The precipitate was filtered off and recrystallised from light petroleum (b. p. 60—80°) as needles (2·3 g.), m. p. 97—98°. The picrate, m. p. 128°, on decomposition gave a purer product, crystallising from light petroleum as prisms, m. p. 98·5—99·5°.

9-*Acetylfluorene oxime* was obtained from 9-acetylfluorene or 9-1′-acetoxyethylidenefluorene

and crystallised from ethanol as needles, m. p. 167—168° [Found (product from 9-acetylfluorene): C, 81·0; H, 5·8; N, 6·1. $C_{15}H_{13}ON$ requires C, 80·6; H, 5·8; N, 6·3%].

9-*Acetylfluorenyl* 9-*Hydroperoxide*.—On storage, in darkness at 0°, with access to air, 9-acetylfluorene was gradually converted into 9-*acetylfluorenyl* 9-*hydroperoxide* (95% in 12 months). This crystallised from methanol as white prisms, m. p. 123—124° (decomp.) (Found: C, 75·5; H, 5·1; peroxide-O, 6·4. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0; peroxide-O, 6·7%). (Peroxide-oxygen was determined by titration of the iodine liberated from potassium iodide in methanol–acetic acid with 0·1N-sodium thiosulphate.)

9-*Methylfluorene*-9-*carboxylic Acid*.—Through 9-methyl-9-sodiofluorene (from 20 g. of 9-methylfluorene) (Part II, *J.*, 1952, 986) suspended in dry ether (500 c.c.) was passed dry carbon dioxide gas for 5 hr. The precipitated sodium salt, on acidification, gave 9-methylfluorene-9-carboxylic acid (4·5 g.), m. p. 170—171° (flat needles from acetic acid) (Wieland and Probst, *Annalen*, 1937, **530**, 274, give m. p. 168°). 9-Methylfluorene (12 g.), m. p. and mixed m. p. 45—46°, was recovered from the ethereal solution.

9-*Trifluoroacetylfluorene*.—9-Fluorenylsodium (from 21 g. of fluorene), trifluoroacetic anhydride (26 g.), and benzene (50 c.c.) were refluxed for 2 hr. The product was filtered from sodium trifluoroacetate (16·0 g.), and the filtrate evaporated to a viscous oil (22·4 g.), which on repeated crystallisation from light petroleum (b. p. 60—80°) gave fluorene (11·5 g.) and 9-*trifluoroacetylfluorene* (4·85 g.), m. p. 188—189° (hexagonal prisms from light petroleum) [Found: C, 69·0; H, 3·5; F, 20·1%; *M* (Rast), 484. $C_{15}H_9OF_3$ requires C, 68·7; H, 3·4; F, 21·7%; *M*, 262]. Hydrolysis with aqueous-alcoholic N-potassium hydroxide gave a "saponification value" 213 ($C_{15}H_9OF_3$ requires "saponification value" 215); the theoretical amount of fluorene was isolated from the acidified mixture.

*Reaction of* 9-*Methyl*-9-*sodiofluorene with Acetic Anhydride*.—9-Methyl-9-sodiofluorene (from 20 g. of 9-methylfluorene), acetic anhydride (12·5 g.), and benzene (250 c.c.) were mixed at room temperature and refluxed for 4 hr. The product was filtered and the filtrate evaporated. The residual oil, on distillation *in vacuo*, gave 9-methylfluorene (14 g.) and from the residue was obtained by crystallisation from light petroleum (b. p. 60—80°) 9:9′-dimethyldi-9-fluorenyl, prisms, m. p. 209—210° (Found: C, 93·5; H, 6·0. Calc. for $C_{28}H_{22}$: C, 93·85; H, 6·15%) (Vansheidt and Moldavskii, *Ber.*, 1931, **64**, 917, give m. p. 209°).

9-1′-*Propionoxypropylidenefluorene*.—Propionyl chloride (35 c.c.) reacted similarly, giving with 9-fluorenylsodium (from 60 g. of fluorene) a viscous oil (71 g.) which after crystallisation several times from light petroleum (b. p. 60—80°) gave fluorene (25 g.) and 9-1′-*propionoxypropylidenefluorene* (28 g.). The latter, after three crystallisations from light petroleum, had m. p. 69·5—70·5° (pale yellow prisms) (Found: C, 82·1; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). It gave a *picrate* (from acetic acid), m. p. 86—87° (Found: C, 58·7; H, 4·1; N, 8·1. $C_{25}H_{21}O_9N_3$ requires C, 59·2; H, 4·2; N, 8·3%). With 1 mol. of bromine it (1 g.) gave a bromide which decomposed on recrystallisation from light petroleum with the evolution of hydrogen bromide to form 9-*bromo*-9-1′-*propionoxypropenylfluorene* (0·6 g.), m. p. 145·5—146·5° (colourless needles) (Found: C, 63·3; H, 4·7; Br, 22·9. $C_{19}H_{17}O_2Br$ requires C, 63·7; H, 4·8; Br, 22·4%).

*Reaction of* 9-*Fluorenylsodium with Carbonyl Chloride*.—(*a*) 9-Fluorenylsodium (from 60 g. of fluorene) was added portionwise to a solution of carbonyl chloride in benzene (1 l.), cooled in ice water whilst carbonyl chloride was still passing into the solution. The mixture was stored overnight, gradually attaining room temperature, and was then filtered to remove sodium chloride (22 g.). The degassed filtrate on evaporation gave an oil (63·4 g.) which on dilution with light petroleum (b. p. 40—60°) (200 c.c.) deposited a brown solid (10 g.), m. p. 200—220°. The latter on extraction with hot *n*-propanol left a colourless solid which on recrystallisation from benzene gave prisms (5 g.), m. p. 242—243·5°. The propanol solution slowly deposited fluorene-9-carboxylic acid as needles (4 g.), m. p. 231·5—233°. The light petroleum solution (after removal of the brown solid), on evaporation and crystallisation from light petroleum, gave fluorene and an oil (26 g.) which could not be obtained crystalline. The oil, which was probably mainly fluorenyl-9-carbonyl chloride was treated with methanol (50 c.c.) and distilled *in vacuo*, to give methyl fluorene-9-carboxylate (21 g.), m. p. 65—66° (Found: C, 80·7; H, 5·4. Calc. for $C_{15}H_{12}O_2$: C, 80·3; H, 5·4%).

The product, m. p. 242—243·5°, was identified as di-9-fluorenyl ketone (Found: C, 90·1; H, 5·1. Calc. for $C_{27}H_{18}O$: C, 90·5; H, 5·0%) (Blum-Bergmann, *Annalen*, 1930, **484**, 47, gives m. p. 230—232°). Its *oxime* (prepared by Bachmann and Boatner's method, *J. Amer. Chem. Soc.*, 1936, **58**, 2097) had m. p. 230·5—231·5° (Found: C, 86·4; H, 5·2; N, 3·5. $C_{27}H_{19}ON$ requires C, 86·8; H, 5·1; N, 3·7%).

Infra-red examination indicated presence of :CO groups in both high-melting products.

(*b*) 9-Fluorenylsodium (from 60 g. of fluorene) in toluene (400 c.c.) was cooled in ice, and carbonyl chloride (approx. 60 g.) passed through the solution for 6 hr. The mixture was allowed to warm to room temperature overnight, methanol (300 c.c.) added, and the solution stored for a further 20 hr. and filtered. The filtrate, after degassing, was washed with 10% sodium carbonate solution and water and dried. The alkaline washings, on acidification, gave 0·8 g. of *di-9-fluorenyl-9-carboxylic acid*, m. p. (prisms; two crystallisations from acetic acid) 258—259° (decomp.) (Found: C, 86·3; H, 4·8%; equiv., 372. $C_{27}H_{18}O_2$ requires C, 86·5; H, 4·8%; equiv., 374). The ultra-violet spectrum is of the fluorene type (Table).

The filtrate, on evaporation at 100°/20 mm., gave a dark oil (68·5 g.). This was extracted with light petroleum (b. p. 60—80°), the extract evaporated, and the semisolid product (54 g.) distilled *in vacuo*, to give fluorene (16 g.), di-9-fluorenyl (8·4 g.), and methyl fluorene-9-carboxylate (22·5 g.), m. p. 64·5—66° (pale yellow prisms from methanol).

The material (14·2 g.) insoluble in light petroleum was chromatographed to give three products: a solid (4·6 g.) crystallising from benzene as prisms m. p. 160—161° (decomp.), having an ultra-violet spectrum of the fluorene type and giving di-9-fluorenyl ketone on treatment with alcoholic potassium hydroxide; a viscous oil (7 g.); and di-9-fluorenyl ketone (0·5 g.).

*Di-9-fluorenyl-9-carboxylic Acid.*—Di-9-fluorenyl (1·35 g.), sodamide (1·0 g.), and decahydronaphthalene (20 c.c.) were heated under reflux for 4 hr. and the precipitated 9-sodiodi-9-fluorenyl (approx. 1·5 g.) filtered off. Carbon dioxide was passed through a suspension of this in light petroleum (b. p. 100—120°) for 5 hr. and the precipitate filtered off, washed with light petroleum (b. p. 40—60°), dried, and extracted with water. The portion insoluble in water (0·9 g.) was di-9-fluorenyl, and the aqueous solution on acidification gave di-9-fluorenyl-9-carboxylic acid (0·4 g.), m. p. (after two crystallisations from acetic acid) and mixed m. p. 257—259° (decomp.) (Found: C, 86·4; H, 4·7%).

*Reaction of 9-Fluorenylsodium with s-Phthaloyl Chloride.*—9-Fluorenylsodium (from 60 g. of fluorene) and *s*-phthaloyl chloride (55 c.c.) in benzene (400 c.c.) were refluxed for 12 hr. The filtered solution was extracted with 10% aqueous sodium hydroxide (100 c.c.), and the alkaline extract acidified, to give phthalic acid (16·6 g.). The washed and dried benzene solution on evaporation gave a dark residue (74 g.). Crystallised from light petroleum (b. p. 60—80°; 400 c.c.) this gave a red solid (40 g.), and fluorene (33·1 g.) was recovered from the filtrate. The red solid on chromatography on silica gel gave bisdiphenylene-ethylene (0·5 g.), a lustrous green solid (5·3 g.), and a bright yellow solid (18 g.). The green compound, crystallising from toluene as green prisms, m. p. 264—265°, was *2 : 5-di-9′-fluorenylidene-2 : 5-dihydro-3 : 4-benzofuran* (Found: C, 91·5; H, 4·7%; *M*, 452. $C_{34}H_{20}O$ requires C, 91·9; H, 4·5%; *M*, 444). Oxidation with hot chromic acid ($CrO_3$ 1·5 g., $H_2O$ 1·5 c.c., and AcOH 1 c.c.) gave fluorenone, m. p. 79—80° (yellow prisms from benzene). The di-9-fluorenylidene compound (0·9 g.) in carbon tetrachloride (80 c.c.) gave with bromine (1·9 g.) in carbon tetrachloride (60 c.c.) a *tetrabromide*, crystallising from toluene as colourless plates, m. p. 422—425° (Found: C, 54·0; H, 2·7; Br, 42·6. $C_{34}H_{20}OBr_4$ requires C, 53·5; H, 2·6; Br, 42·0%). The ultra-violet spectrum of the tetrabromide was similar in general shape to those of other 9-bromofluorenes.

The bright yellow solid, *3-9′-fluorenylidenephthalide*, crystallised from *n*-propanol as bright yellow needles, m. p. 212—214° (Found: C, 85·0; H, 4·1%; sap. val., 195. Calc. for $C_{21}H_{12}O_2$: C, 85·1; H, 4·1%; sap. val. 189) (Wislicenus and Neber, *loc. cit.*, give m. p. 204—206°). Hydrolysis with alcoholic potassium hydroxide gave an acid which on recrystallisation from acetic acid gave *9-1′-o-carboxybenzoylfluorene* prisms, m. p. 201—202° (decomp.) (Found: C, 79·7; H, 4·5%, equiv., 320. Calc. for $C_{21}H_{14}O_3$: C, 80·0; H, 4·5%; equiv., 314) (Wislicenus and Neber, *loc. cit.*, give m. p. 188—189°). 3-9′-Fluorenylidenephthalide (0·5 g.) gave a *dibromide* (0·4 g.) which crystallised from benzene as prisms, m. p. 199—200° (decomp.) (Found: C, 55·7; H, 2·7; Br, 34·7. $C_{21}H_{12}O_2Br_2$ requires C, 55·3; H, 2·6; Br, 35·1%).

*Reaction of 9-Fluorenylsodium with Phthalic Anhydride.*—9-Fluorenylsodium (from 60 g. of fluorene) and phthalic anhydride (57 g.) in benzene (400 c.c.) were refluxed for 12 hr. The product, worked up as in the previous experiment, gave fluorene (36 g.), bisdiphenylene-ethylene (0·5 g.), 2 : 5-di-9′-fluorenylidene-2 : 5-dihydro-3 : 4-benzofuran (2 g.), and 3-9′-fluorenylidenephthalide (12 g.).

*Reaction of 9-Fluorenylsodium with Naphthalic Anhydride.*—9-Fluorenylsodium (from 40 g. of fluorene) and naphthalic anhydride (50 g.) in benzene (500 c.c.) were refluxed for 8 hr. The product was filtered, to remove disodium naphthalate (40 g.) and other insoluble material (28 g.). The filtrate on evaporation left an oil (26·5 g.). The last two materials were combined and chromatographed on silica gel, to give fluorene (22 g.), naphthalic anhydride (5·5 g.), *3-9′-fluorenylidenenaphthalide* (IV) (Found: C, 87·2; H, 4·1%; *M*, 340. $C_{25}H_{14}O_2$

requires C, 86·7; H, 4·0%; *M*, 346), deep red, m. p. 256—257° (prisms from benzene) (1·9 g.), and a colourless *fluorene-9'*-spiro-2-*perinaphthane*-1 : 3-*dione* (Found : C, 87·1; H, 4·1. $C_{25}H_{14}O_2$ requires C, 86·7; H, 4·0%), m. p. 282—284° (recrystallised from benzene as white needles) (10·4 g.).

The red solid had an infra-red spectrum showing a band due to the C=O group in the region expected for a lactone or a saturated or unsaturated ester. This substance in carbon tetrachloride absorbed 1 mol. of bromine, the solution losing its colour; evaporation followed by crystallisation gave pale yellow prisms, m. p. 210—212°, which contained bromine but did not give correct analyses for the dibromide and have not been identified.

The spiran had infra-red bands due to the C=O group in the region expected for ketones. It gave a *dioxime*, m. p. 287—287·5° (Found : N, 7·2. $C_{25}H_{16}O_2N_2$ requires N, 7·4%). With boiling phenylhydrazine fission occurred, to give *N'*-phenyl-*NN*-naphthalohydrazide (m. p. and mixed m. p. 219—220°) and fluorene.

*Reaction of 9-Fluorenylsodium with Succinic Anhydride.*—9-Fluorenylsodium (from 60 g. of fluorene) and succinic anhydride (38·5 g.) in benzene (400 c.c.) were refluxed for 12 hr. The product was filtered from sodium succinate (35 g.) and other insoluble material (10·5 g.). The filtrate on evaporation of the benzene left partly solid residue (57·2 g.). The last two materials were chromatographed on silica gel, to give fluorene (34·3 g.), bisdiphenylene-ethylene (0·5 g.), di-9-fluorenyl (4·3 g.), 2 : 5-*di*-9'-*fluorenylidenetetrahydrofuran* (1·48 g.), red needles (from toluene), m. p. 314—315° (Found : C, 90·8; H, 5·1%; *M*, 400. $C_{30}H_{20}O$ requires C, 90·9; H, 5·05%; *M*, 396), and a white solid (5·6 g.).

Bromine (in carbon tetrachloride) at 0° added readily to the red compound (in carbon tetrachloride), and a white bromide was precipitated [m. p. *ca.* 360° (decomp.)]. Recrystallisation of this from benzene resulted, however, in decomposition, with evolution of hydrogen bromide and bromine to a bronze-green metallic *substance*, m. p. 314—316° (Found : C, 90·9; H, 4·65. $C_{30}H_{18}O$ requires C, 91·3; H, 4·57%).

The white solid crystallised from benzene as needles, m. p. 212—213°, and had an ultra-violet spectrum of the 9-ethylidenefluorene type (see Table). The infra-red spectrum shows bands due to the C:O group, probably as a lactone, the compound being *γ*-9-*fluorenylidene*-*γ*-*butyrolactone* (Found : C, 82·5; H, 4·9. $C_{17}H_{12}O_2$ requires C, 82·25; H, 4·8%). Hydrolysis by boiling for ½ hr. with alcoholic N-potassium hydroxide gave *γ*-9-*fluorenyl*-*γ*-*oxobutyric acid*, m. p. 154—155° (Found : C, 76·2; H, 5·4%; equiv., 268. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%; equiv., 266). The lactone forms a *picrate* (yellow needles, m. p. 177·5—180°) in acetic acid (Found : C, 57·75; H, 3·2; N, 8·6. $C_{23}H_{15}O_9N_3$ requires C, 57·9; H, 3·2; N, 8·8%), and with 1 mol. of bromine gives a *dibromide*, m. p. 110—111° (decomp.) (prisms from light petroleum) (Found : C, 49·8; H, 2·9; Br, 38·9. $C_{17}H_{12}O_2Br_2$ requires C, 50·0; H, 2·9; Br, 39·2%), the ultra-violet spectrum of which is of the 9-bromofluorene type.

*Reaction of 9-Fluorenylsodium with Succinyl Chloride.*—9-Fluorenylsodium (from 50 g. of fluorene) and succinyl chloride (24·5 g.) in benzene (400 c.c.) were refluxed for 12 hr. The product was filtered from sodium chloride (19·0 g.), and the filtrate evaporated to a brown solid (52 g.). Chromatography on silica gel gave fluorene (32·0 g.), bisdiphenylene-ethylene (1·1 g.), di-9-fluorenyl (5·4 g.), and the above lactone (6·3 g.).

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9-Ethylidenefluorene ..... | $\lambda_{max.}$, Å | 2300 | 2465 | 2555 | 2710 | 2800 | 2970 | 3110 |
| | log ε | 4·61 | 4·46 | 4·60 | 4·13 | 4·15 | 4·03 | 4·00 |
| 9-1'-Acetoxyethylidenefluorene ..... | $\lambda_{max.}$, Å | 2300 | 2475 | 2550 | 2675 | 2750 | 3000 | 3125 |
| | log ε | 4·60 | 4·46 | 4·56 | 4·19 | 4·20 | 4·07 | 4·07 |
| 9-1'-Propionoxypropylidenefluorene | $\lambda_{max.}$, Å | 2300 | 2475 | 2550 | 2700 | 2800 | 3000 | 3125 |
| | log ε | 4·60 | 4·47 | 4·54 | 4·20 | 4·21 | 4·10 | 4·12 |
| *γ*-9-Fluorenylidene-*γ*-butyrolactone | $\lambda_{max.}$, Å | 2325 | 2475 | 2575 | 2750 | 2850 | 3025 * | 3200 |
| | log ε | 4·56 | 4·27 | 4·31 | 4·19 | 4·14 | 3·92 | 3·93 |
| Fluorene ..... | $\lambda_{max.}$, Å | 2260 * | 2545 * | 2610 | 2710 * | 2885 | 3000 | |
| | log ε | 3·86 | 4·20 | 4·24 | 4·10 | 3·78 | 3·94 | |
| Di-9-fluorenyl-9-carboxylic acid ... | $\lambda_{max.}$, Å | 2375 * | 2600 * | 2675 | — | 2935 | 3050 | |
| | log ε | 4·31 | 4·39 | 4·44 | — | 3·95 | 4·00 | |

* Inflection.

*Absorption Spectra.*—Ultra-violet absorption spectra (see Table) were determined in absolute ethanol with a Hilger "Uvispek" spectrophotometer. Infra-red absorption spectra were measured with a Grubb Parsons S3A single-beam spectrometer, the powdered specimens being suspended in "Nujol."

We thank Mr. W. G. Wilman for the ultra-violet and infra-red examinations, Mr. G. A. Vaughan for analyses, and Mr. R. Belcher for the fluorine determination on 9-trifluoroacetylfluorene. We are grateful to the Council of the Coal Tar Research Association and to the Department of Scientific and Industrial Research for permission to publish this work.

THE COAL TAR RESEARCH ASSOCIATION,
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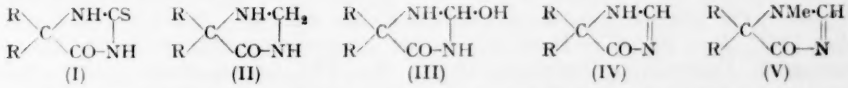
## 618. *Thiohydantoins. Part IV.* The Action of Raney Nickel on Some Monothiohydantoins.*

By H. C. CARRINGTON, C. H. VASEY, and W. S. WARING.

The hydrogenolysis of some 5 : 5-disubstituted 2- and 4-thiohydantoins and their *N*-methyl derivatives by use of Raney nickel in alcohol, to give the di- and tetra-hydroglyoxalines, has been examined, and the structures of the products have been determined. In some cases the 2-thiohydantoins yielded 2-hydroxy- or 2-alkoxy-tetrahydroglyoxalines.

THE preparation of tetrahydro-4-oxo-5 : 5-diphenylglyoxaline (II; R = Ph) by the reduction of 5 : 5-diphenyl-2-thiohydantoin (I; R = Ph) with sodium in amyl alcohol was described by Biltz and Seydel (*Annalen*, 1912, **391**, 215). On oxidation of (II; R = Ph) with alkaline permanganate the initial product was tetrahydro-2-hydroxy-4-oxo-5 : 5-diphenylglyoxaline (III; R = Ph), which when heated above its melting point gave a dihydro-4-oxo-5 : 5-diphenylglyoxaline to which was ascribed the formula (IV; R = Ph). The dihydro-derivative, with methyl sulphate in aqueous alkali, gave a monomethyl derivative of m. p. 177°, which was formulated as (V; R = Ph) because on alkaline hydrolysis it gave a product of m. p. 211°, considered by Biltz and Seydel to be α-methylaminodiphenylacetic acid.



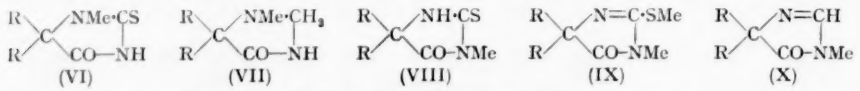

We have now found that reductive removal of sulphur from 5 : 5-disubstituted monothiohydantoins is easily effected by the action of Raney nickel in ethanol, and when the necessary *N*- and *S*-methyl derivatives of the 5 : 5-diphenylmonothiohydantoins became available (Carrington and Waring, *J.*, 1950, 354) it was possible to check the structure of the compounds described by Biltz and Seydel. The conversion of 5-phenyl-2 : 4-dithiohydantoin by Raney nickel into 4-phenylglyoxaline has been reported by Cook, Heilbron, and Levy (*J.*, 1947, 1598) and while the present work was in progress Stanek (*Chem. Listy*, 1951, **45**, 459) described briefly the action of Raney nickel on 5 : 5-diphenyl-2-thiohydantoin with the formation of the compound (II; R = Ph) obtained by Biltz and Seydel.

5 : 5-Diphenyl-2-thiohydantoin, when heated in ethanol with Raney nickel, gave tetrahydro-4-oxo-5 : 5-diphenylglyoxaline, identical with that described by Biltz and Seydel, and the oxidation to the dihydro-compound and methylation of this proceeded smoothly according to their description. When 1-methyl-5 : 5-diphenyl-2-thiohydantoin (VI; R = Ph) was treated with Raney nickel in a similar way, the crude product was usually a mixture of the di- and the tetra-hydroglyoxaline derivative. The compounds were best obtained pure by oxidation or further reduction of the crude mixture. 1 : 4-Dihydro-1-methyl-4-oxo-5 : 5-diphenylglyoxaline (V; R = Ph) obtained by oxidation in this way had m. p. 231°, and was clearly not identical with the product of m. p. 177° to which this structure had previously been assigned. The corresponding tetrahydro-1-methyl-4-oxo-5 : 5-diphenylglyoxaline (VII; R = Ph), obtained from the crude reaction product by further reduction, had m. p. 215—216°. Furthermore, both 3-methyl-5 : 5-

* Part III, *J.*, 1950, 354.

diphenyl-2-thiohydantoin (VIII; R = Ph) and its *S*-methyl derivative (IX; R = Ph), on treatment with Raney nickel in ethanol gave **3 : 4-dihydro-3-methyl-4-oxo-5 : 5-diphenylglyoxaline** (X; R = Ph), which proved to be identical with the methyl derivative, m. p. 177°.

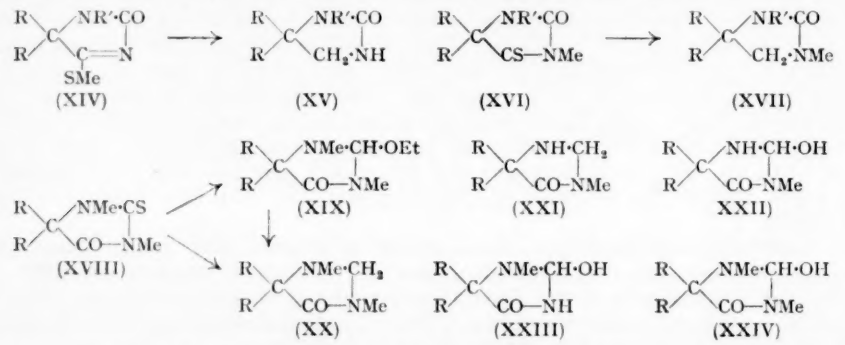
It was then necessary to elucidate the true course of the alkaline hydrolysis of (X; R = Ph). This reaction, carried out by Biltz and Seydel's method, gave in our hands a




crystalline product of m. p. 216°, which by analysis appeared to be α-formamidodiphenylacetic acid (XI; R = Ph), this being confirmed by further acid hydrolysis to α-aminodiphenylacetic acid (XII; R = Ph), m. p. 263° (decomp.). Biltz and Seydel, who prepared this acid by hydrolysis of (II; R = Ph), gave m. p. 244—245°.

It is thus clear that Biltz and Seydel's dihydro-oxodiphenylglyoxaline is (XIII; R = Ph), and that methylation takes place at the 3-position.

By the action of Raney nickel on other *N*- and *S*-methyl derivatives of the 5 : 5-diphenylmonothiohydantoins most of the corresponding oxoglyoxalines have been prepared. Thus the methylthio-compounds (XIV; R = Ph, R′ = H or Me) gave the tetrahydroglyoxalines (XV; R = Ph, R′ = H or Me, respectively) and the 3-methyl- and 1 : 3-dimethyl-4-thiohydantoins (XVI; R = Ph, R′ = H or Me), gave the tetrahydroglyoxalines (XVII; R = Ph, R′ = H or Me, respectively). 1 : 3-Dimethyl-5 : 5-diphenyl-2-thiohydantoin (XVIII; R = Ph) gave either 2-ethoxytetrahydro-1 : 3-dimethyl-4-oxo-5 : 5-diphenylglyoxaline (XIX; R = Ph) or tetrahydro-1 : 3-dimethyl-4-oxo-5 : 5-diphenylglyoxaline (XX; R = Ph) according to the conditions of the reaction. However, attempts to oxidise (XV; R = Ph, R′ = H or Me) to the corresponding dihydro-derivatives were unsuccessful. Catalytic hydrogenation of (X; R = Ph), Adams catalyst being used in ethanol, gave tetrahydro-3-methyl-4-oxo-5 : 5-diphenylglyoxaline (XXI; R = Ph).




In the removal of sulphur from 5 : 5-pentamethylene-2-thiohydantoin (I; RR = $[CH_2]_5$) and its derivatives by Raney nickel there was a much greater tendency for the formation of 2-hydroxy-derivatives. Thus, (I; RR = $[CH_2]_5$) gave as the main product tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline (III; RR = $[CH_2]_5$), with only a small amount of tetrahydro-4-oxo-5 : 5-pentamethyleneglyoxaline (II; RR = $[CH_2]_5$). Similarly, 3-methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII; RR = $[CH_2]_5$) gave (XXII; RR = $[CH_2]_5$) together with a small yield of (XXI; RR = $[CH_2]_5$); and (VI; RR = $[CH_2]_5$) gave (XXIII; RR = $[CH_2]_5$). Hydroxy-derivatives were not obtained on

reduction of 5 : 5-pentamethylene-4-thiohydantoin and its 3-methyl derivative, which gave the corresponding tetrahydro-2-oxoglyoxalines.

Some consideration has been given to the true nature of these 2-hydroxy-derivatives. Above its melting point, that obtained by the permanganate oxidation of tetrahydro-4-oxo-5 : 5-diphenylglyoxaline lost water, and the dihydroglyoxaline so formed was reconverted in boiling water into the tetrahydro-2-hydroxy-derivative, so that the possibility that the latter is a simple hydrate could not immediately be excluded. However, the melting point of a mixture of the two compounds was below that of either individual, and their infra-red absorption spectra showed greater differences than are common in the spectra of hydrated and anhydrous organic compounds. Further and more cogent evidence that we were dealing with true hydroxy-derivatives was obtained in the 5 : 5-pentamethylene series. Tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline (III; RR = $[CH_2]_5$) was unchanged on prolonged drying in a vacuum at 120°. Its infra-red absorption spectrum showed no band between 3500 and 3700 cm.$^{-1}$ where water might be expected to absorb. At its melting point (170°) it effervesced with loss of water, but profound decomposition occurred and no characterisable product could be isolated. Dehydration could be brought about, however, by acetic anhydride, and gave dihydro-4-oxo-5 : 5-pentamethyleneglyoxaline (XIII; RR = $[CH_2]_5$), which crystallised unchanged from hot water.

1 : 3-Dimethyl-5 : 5-pentamethylene-2-thiohydantoin, on treatment with Raney nickel, gave tetrahydro-2-hydroxy-1 : 3-dimethyl-4-oxo-5 : 5-pentamethyleneglyoxaline (XXIV; RR = $[CH_2]_5$). In this case a hydrated dihydroglyoxaline structure is clearly impossible. A similar example, the formation of tetrahydro-2-ethoxy-1 : 3-dimethyl-4-oxo-5 : 5-diphenylglyoxaline (XIX; R = Ph) from 1 : 3-dimethyl-5 : 5-diphenyl-2-thiohydantoin has already been mentioned.

With one exception all the crystalline products obtained by the action of Raney nickel on the 5-methyl-5-phenylmonothiohydantoins have been the normal tetrahydro-oxoglyoxalines. Thus, 5-methyl-5-phenyl-2-thiohydantoin and 5-methyl-5-phenyl-4-thiohydantoin gave the tetrahydro-4-oxoglyoxaline (II; R, R = Me, Ph) and the tetrahydro-2-oxoglyoxaline (XV; R, R = Me, Ph; R′ = H) respectively. The corresponding 1-methyl-2-thiohydantoin and the 3-methyl-4-thiohydantoin gave (VII; R, R = Me, Ph) and (XVII; R, R = Me, Ph; R′ = H) respectively. The only crystalline product obtained from the reaction of Raney nickel with 1 : 3 : 5-trimethyl-5-phenyl-2-thiohydantoin was *N*-methyl-α-phenylpropionamide. 3 : 5-Dimethyl-5-phenyl-2-thiohydantoin gave an oil, for which no satisfactory analysis has been obtained.

## Experimental

*Hydrogenolysis : General Procedure.*—The thiohydantoin (0·04 mole) in ethanol (250 c.c.) was heated under reflux with Raney nickel (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695) (*ca.* 12 c.c. of the settled sludge) for 2—5 hr. until a filtered test specimen of the solution was sulphur-free. The mixture was filtered through kieselguhr while hot and the filtrate concentrated *in vacuo*. The residue usually crystallised and was recrystallised from alcohol or water.

The compounds shown in the table were prepared from the corresponding monothiohydantoins and their derivatives by this procedure. Exceptions and special preparations are referred to in the notes. The yields quoted are of the purified products and depend largely on the ease of isolation of the product. Some of the monothiohydantoins used have been described in earlier papers of this series and elsewhere. New preparations required for this work are described on p. 3110.

*Note* 1 (to Table). Hydrogenolysis of 5 : 5-diphenyl-2-thiohydantoin gave tetrahydro-4-oxo-5 : 5-diphenylglyoxaline (II; R = Ph), previously described by Biltz and Seydel (*Annalen*, 1912, **391**, 215) as having m. p. 175—176°. Permanganate oxidation under conditions given by these authors yielded (III; R = Ph) which at 190° was converted into (XIII; R = Ph) to which Biltz and Seydel ascribed structure (IV). They also reported the preparation of (X; R = Ph) [to which they attributed structure (V)], m. p. 166—167°, by methylation of (XIII; R = Ph).

*Note* 2. (X; R = Ph) was prepared (66% yield) from 3 : 4-dihydro-3-methyl-2-methyl-

thio-4-oxo-5 : 5-diphenylglyoxaline (IX; R = Ph) by hydrogenolysis, and also from 3 : 4-dihydro-4-oxo-5 : 5-diphenylglyoxaline (XIII; R = Ph) by methylation with methyl sulphate and sodium hydroxide.

*Note* 3. The crude product from the hydrogenolysis of 1-methyl-5 : 5-diphenyl-2-thiohydantoin was a mixture of the di- (V; R = Ph) and the tetra-hydroglyoxaline (VII; R = Ph). These could with difficulty be separated by fractional crystallisation from ethanol, the dihydro-derivative being the less soluble. They were also prepared separately by (*a*) oxidation and (*b*) reduction of the crude mixture :

(*a*) The crude mixture (12 g. from 25 g. of the thiohydantoin) was suspended in water, made alkaline with sodium hydroxide solution, and heated to 80—90°. Potassium permanganate (2% solution) was added until the violet colour persisted, and, after cooling, the brown solid was filtered off and extracted with boiling ethanol. Concentration of the extract gave colourless crystals, m. p. 226—228° (3·5 g.), of 1 : 4-dihydro-1-methyl-4-oxo-5 : 5-diphenylglyoxaline (V; R = Ph). Recrystallisation from ethanol raised this to m. p. 231°.

(*b*) The crude mixture (13 g. from 25 g. of the thiohydantoin) was reduced in ethanol at room temperature with hydrogen at 50 lb./sq. in. and Raney nickel. The resulting suspension

| | M. p. | Yield (%) | Formula | Required (%): C | H | N | Found (%): C | H | N | Note (p. 3107) |
|---|---|---|---|---|---|---|---|---|---|---|
| (II; R = Ph) | 181—182° | 64 | $C_{15}H_{14}ON_2$ | — | — | — | — | — | — | 1 |
| (II; R = *p*-MeO·$C_6H_4$) | 162 | 22 | $C_{17}H_{18}O_2N_2$ | 68·45 | 6·0 | 9·4 | 68·6 | 6·1 | 9·6 | |
| (II; R, R = Ph, Me) | 119 | 21 | $C_{10}H_{12}ON_2$ | 68·2 | 6·8 | 15·9 | 67·8 | 6·9 | 15·6 | |
| (II; R, R = Ph, Et) | 142—143 | 46 | $C_{11}H_{14}ON_2$ | 69·5 | 7·4 | 14·7 | 69·3 | 7·3 | 14·2 | |
| (II; RR = $[CH_2]_5$) | 157 | — | $C_8H_{14}ON_2$ | 62·3 | 9·1 | 18·2 | 62·1 | 9·1 | 18·6 | 7 |
| (III; R = Ph) | 189 | — | $C_{15}H_{14}O_2N_2$ | 70·8 | 5·5 | 11·0 | 71·0 | 5·5 | 11·0 | 1 |
| (III; R = Me) | 169 | 39 | $C_5H_{10}O_2N_2$ | 46·2 | 7·7 | 21·5 | 46·2 | 7·8 | 20·2 | |
| (III; RR = $[CH_2]_4$) | 194 | 26 | $C_7H_{12}O_2N_2$ | 53·9 | 7·7 | 17·95 | 53·9 | 7·6 | 18·3 | |
| (III; RR = $[CH_2]_5$) | 169—170 | 40 | $C_8H_{14}O_2N_2$ | 56·6 | 8·2 | 16·5 | 56·5 | 8·3 | 16·4 | |
| (III; RR = $[CH_2]_2$·CHMe·$[CH_2]_2$) | 182—183 | 43 | $C_9H_{16}O_2N_2$ | 58·7 | 8·7 | 15·2 | 58·9 | 8·3 | 15·0 | |
| (V; R = Ph) | 231 | 16 | $C_{15}H_{14}ON_2$ | 76·8 | 5·6 | 11·2 | 77·2 | 5·8 | 11·0 | 3 |
| (V; RR = $[CH_2]_5$) | B. p. 85°/ 0·1 mm. | 67 | $C_9H_{14}ON_2$ | 65·1 | 8·4 | 16·9 | 65·5 | 8·7 | 16·5 | 12 |
| (VII; R = Ph) | 215—216 | 41 | $C_{15}H_{16}ON_2$ | 76·1 | 6·35 | 11·1 | 76·1 | 6·4 | 11·0 | 3 |
| (VII; R, R = Ph, Me) | 130—131 | 10 | $C_{11}H_{14}ON_2$ | 69·5 | 7·4 | 14·7 | 69·4 | 7·4 | 14·9 | |
| (X; R = Ph) | 176—177 | 71 | $C_{15}H_{14}ON_2$ | 76·8 | 5·6 | 11·2 | 76·6 | 5·9 | 10·9 | 1, 2 |
| (X; RR = $[CH_2]_5$) | B. p. 67°/ 14 mm. | 92 | $C_9H_{14}ON_2$ | 65·1 | 8·4 | 16·9 | 64·7 | 8·3 | 16·95 | 13 |
| (XIII; R = Ph) | 169—170 | — | $C_{15}H_{12}ON_2$ | 76·2 | 5·1 | 11·9 | 76·1 | 5·0 | 11·7 | 1 |
| (XIII; RR = $[CH_2]_5$) | 94—95 | 32 | $C_8H_{12}ON_2$ | 63·2 | 7·9 | 18·4 | 63·3 | 7·7 | 18·6 | 11 |
| (XV; R = Ph; R′ = H) | 252—253 | 45 | $C_{15}H_{14}ON_2$ | 75·6 | 5·9 | 10·75 | 75·5 | 5·9 | 10·7 | 5 |
| (XV; R, R = Ph, Me; R′ = H) | 200—201 | 60 | $C_{10}H_{12}ON_2$ | 68·2 | 6·8 | 15·9 | 68·5 | 6·8 | 16·0 | |
| (XV; RR = $[CH_2]_5$; R′ = H) | 221—222 | 61 | $C_8H_{14}ON_2$ | 62·3 | 9·1 | 18·2 | 62·6 | 9·0 | 18·1 | |
| (XV; R = Ph; R′ = Me) | 178—180 | 55 | $C_{16}H_{16}ON_2$ | 76·2 | 6·35 | 11·1 | 76·3 | 6·4 | 11·1 | 5 |
| (XVII; R = Ph, R′ = H) | 254—256 | 56 | $C_{16}H_{16}ON_2$ | 76·2 | 6·35 | 11·1 | 76·3 | 6·45 | 11·2 | |
| (XVII; RR = Ph, Me; R′ = H) | 130 | 44 | $C_{11}H_{14}ON_2$ | 69·5 | 7·4 | 14·7 | 69·3 | 7·2 | 14·1 | |
| (XVII; RR = $[CH_2]_5$; R′ = H) | 126—127 | 46 | $C_9H_{14}ON_2$ | 64·3 | 9·5 | 16·7 | 64·4 | 9·3 | 17·0 | |
| (XVII; R = Ph, R′ = Me) | 106—108 | 43 | $C_{17}H_{18}ON_2$ | 76·8 | 6·75 | 10·5 | 76·0 | 6·7 | 10·2 | |
| (XIX; R = Ph) | 128—130 | 38 | $C_{19}H_{22}O_2N_2$ | 73·7 | 7·1 | 9·0 | 73·8 | 7·2 | 8·8 | 4 |
| (XX; R = Ph) | 113—115 | 48 | $C_{17}H_{18}ON_2$ | 76·8 | 6·75 | 10·5 | 76·0 | 6·85 | 9·75 | |
| (XXI; R = Ph) | 86—87 | 85 | $C_{16}H_{16}ON_2$ | 76·2 | 6·35 | 11·1 | 76·0 | 6·1 | 11·0 | 6 |
| (XXI; RR = $[CH_2]_5$) | 75 | 16 | $C_9H_{16}ON_2$ | 64·3 | 9·5 | 16·7 | 64·2 | 9·3 | 16·6 | 9 |
| (XXII; RR = $[CH_2]_5$) | 144 | 17 | $C_9H_{16}O_2N_2$ | 58·7 | 8·7 | 15·2 | 58·7 | 8·8 | 14·6 | 8 |
| (XXIII; RR = $[CH_2]_5$) | 160—161 | 55 | $C_9H_{16}O_2N_2$ | 58·7 | 8·7 | 15·2 | 58·8 | 8·4 | 15·4 | |
| (XXIV; RR = $[CH_2]_5$) | 92—93 | 7 | $C_{10}H_{18}O_2N_2$ | 60·6 | 9·1 | 14·15 | 60·4 | 8·7 | 14·05 | 10 |

was filtered at the b. p. Concentration of the filtrate yielded tetrahydro-1-methyl-4-oxo-5 : 5-diphenylglyoxaline, m. p. 212° (9·3 g.), raised by crystallisation from ethanol to 215—216°.

*Note* 4. *Hydrogenolysis of* 1 : 3-*dimethyl*-5 : 5-*diphenyl*-2-*thiohydantoin* (XVIII; R = Ph). 1 : 3-Dimethyl-5 : 5-diphenyl-2-thiohydantoin subjected to the general hydrogenolysis procedure (2·5 hr.) gave a product which, according to analyses, was 2-ethoxytetrahydro-1 : 3-dimethyl-4-oxo-5 : 5-diphenylglyoxaline (XIX; R = Ph). When this experiment was repeated with methanol, propanol, or *cyclo*hexane in place of ethanol, tetrahydro-1 : 3-dimethyl-4-oxo-5 : 5-diphenylglyoxaline (XX; R = Ph) was obtained. The 2-ethoxy-compound (XIX; R = Ph), with Raney nickel in ethanol under reflux (3 hr.), gave mainly (XX; R = Ph), with a small amount of *N-methyl-αx-diphenylacetamide*, m. p. 165—166°, identical with an authentic

sample prepared from diphenylacetyl chloride and aqueous methylamine (Found: C, 80·0; H, 6·65; N, 6·2. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·65; N, 6·2%).

*Note* 5. Attempted oxidation of (XV; R = Ph, R′ = H or Me) with potassium permanganate solution at 90—100° yielded only starting material although some of the oxidising agent was taken up. Attempted oxidations by bromine in boiling acetic acid and by aqueous sodium hypobromite solution were also unsuccessful.

*Note* 6. Catalytic reduction of 3 : 4-dihydro-3-methyl-5 : 5-diphenyl-4-oxoglyoxaline (X; R = Ph) in ethanol at 100° with Adams catalyst and hydrogen at 100 atm. gave tetrahydro-3-methyl-4-oxo-5 : 5-diphenylglyoxaline (XXI; R = Ph), m. p. 86—87° (from ether).

*Note* 7. The alcoholic mother-liquors from the recrystallisation of (III; RR = $[CH_2]_5$) on long storage deposited (II; RR = $[CH_2]_5$) as colourless diamond-shaped plates.

*Note* 8. The waxy solid obtained on removal of the alcohol was triturated with ether, to give (XXII; RR = $[CH_2]_5$) as a white insoluble powder.

*Note* 9. Evaporation of the ethereal washings from the puification of (XXII; RR = $[CH_2]_5$) (Note 8) yielded (XXI; RR = $[CH_2]_5$) as colourless plates.

*Note* 10. The oil obtained after removal of the alcohol crystallised after some days. The crystals were washed with ether before recrystallisation from ether.

*Note* 11. *Dihydro-4-oxo-5 : 5-pentamethyleneglyoxaline* (XIII; RR = $[CH_2]_5$). Tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline (III; RR = $[CH_2]_5$) (2 g.) and acetic anhydride (20 c.c.) were heated under reflux for 1 hr. Removal of the acetic acid and anhydride *in vacuo* left an oil which solidified on cooling. Trituration with ether yielded the product as an insoluble powder (0·6 g.) which crystallised from a small amount of benzene as colourless plates.

*Note* 12. *Dihydro-1-methyl-4-oxo-5 : 5-pentamethyleneglyoxaline* (V; RR = $[CH_2]_5$). Tetrahydro-2-hydroxy-1-methyl-4-oxo-5 : 5-pentamethyleneglyoxaline (XXIII; RR = $[CH_2]_5$) (1·0 g.) and acetic anhydride (10 c.c.) were heated under reflux for 1 hr. and then the acetic acid and excess of anhydride removed by distillation *in vacuo*. The product distilled as a colourless mobile liquid, $n_D^{22}$ 1·4983.

*Note* 13. *Dihydro-3-methyl-4-oxo-5 : 5-pentamethyleneglyoxaline* (X; RR = $[CH_2]_5$). Dihydro-4-oxo-5 : 5-pentamethyleneglyoxaline (XIII; RR = $[CH_2]_5$) (0·9 g.), methyl iodide (10 c.c.), and silver oxide (1·0 g.) were heated under reflux for 5 hr. The mixture was filtered while hot and the methyl iodide removed by distillation. The residue distilled as a colourless mobile liquid (0·75 g.), $n_D^{22}$ 1·4672, having a sweet smell. In a few days it became viscous and yellow.

*Alkaline Hydrolysis of 3 : 4-Dihydro-3-methyl-4-oxo-5 : 5-diphenylglyoxaline* (X; R = Ph).—3 : 4-Dihydro-3-methyl-4-oxo-5 : 5-diphenylglyoxaline (1 g.) was heated under reflux for 2 hr. with 33% aqueous potassium hydroxide (4 c.c.) and ethanol (30 c.c.). Ammonia was evolved. The solvent was removed *in vacuo* and water (50 c.c.) added. The solution was almost neutralised by carbon dioxide and then clarified by filtration through "Filtercel." Acidification of the filtrate at 50—60° yielded *α-formamidodiphenylacetic acid* (XI; R = Ph) (0·45 g.), m. p. 200—202°, raised by crystallisation from ethanol to 216° (Found: C, 70·3; H, 5·1; N, 5·7. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%).

This acid (1 g.) was heated under reflux for 70 min. with a mixture of concentrated hydrochloric acid (20 c.c.) and water (8 c.c.). On cooling and neutralisation to pH 7 with sodium hydroxide solution, *α-aminodiphenylacetic acid* separated and was recrystallised from 50% ethanol, giving colourless needles, m. p. 263° (decomp.) (Found: C, 73·8; H, 5·8; N, 6·1. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%).

*Methylation of Tetrahydro-2-oxo-5 : 5-pentamethyleneglyoxaline* (XV; RR = $[CH_2]_5$, R′ = H).—Tetrahydro-2-oxo-5 : 5-pentamethyleneglyoxaline (3·3 g.), methyl iodide (50 c.c.), and silver oxide (3·0 g.) were heated under reflux for 5 hr. then filtered while hot, and the methyl iodide was removed by distillation. The residue was dissolved in ether, the extract filtered from some unchanged starting material, and the ether removed. The residual *3-methyl* derivative (2·2 g.) crystallised, and was recrystallised from water, giving large square plates, m. p. 126—127° (Found: C, 64·4; H, 9·5; N, 17·0. $C_9H_{16}ON_2$ requires C, 64·3; H, 9·5; N, 16·7%). A mixed m. p. with (XVII; RR = $[CH_2]_5$, R′ = H) prepared by hydrogenolysis of 3-methyl-5 : 5-pentamethylene-4-thiohydantoin was undepressed.

*Action of Thionyl Chloride on Tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline* (III; RR = $[CH_2]_5$).—Tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline (2·0 g.) and thionyl chloride (4 c.c.) were warmed at 55° for 10 min. When the vigorous reaction was over, the excess of thionyl chloride was removed *in vacuo* and methanol added to the remaining

gum. The solid which separated was recrystallised from a little methanol from which 1-cyano-*cyclo*hexylamine hydrochloride was obtained as large colourless plates, m. p. 194—195° (decomp.) (0·3 g.) (Found: C, 52·05; H, 7·65; N, 17·9; Cl, 20·9. Calc. for $C_7H_{13}N_2Cl$: C, 52·35; H, 8·1; N, 17·45; Cl, 22·1%). Snessarew (*J. pr. Chem.*, 1914, **89**, 369) records m. p. 189° (decomp.).

*Action of Raney Nickel on* 1 : 3 : 5-*Trimethyl-5-phenyl-2-thiohydantoin.*—1 : 3 : 5-Trimethyl-5-phenyl-2-thiohydantoin (2·0 g.) in ethanol (50 c.c.) was heated under reflux with Raney nickel for 5 hr.; it was then sulphur-free. The mixture was filtered, and the solvent removed. The residual thick oil crystallised after 5 weeks, and the waxy solid was pressed on a porous tile. Crystallisation from aqueous methanol yielded N-*methyl-α-phenylpropionamide*, m. p. 82°, undepressed on admixture with a sample, m. p. 82°, prepared from α-phenylpropionyl chloride and methylamine (Found: C, 73·0; H, 7·6; N, 8·5. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%).

*Benzoylation of Tetrahydro-2-hydroxy-4-oxo-5* : 5-*pentamethyleneglyoxaline* (III; RR = $[CH_2]_5$).—Tetrahydro-2-hydroxy-4-oxo-5 : 5-pentamethyleneglyoxaline (1·0 g.) was added to dry dioxan (30 c.c.) and excess of sodium wire. On warming, the compound dissolved and formed an insoluble sodio-derivative. Benzoyl chloride (1 c.c.) was added to the cooled mixture, which was then left for 12 hr. The mixture was filtered, the filtrate evaporated *in vacuo*, and the solid residue recrystallised from methanol. The product was obtained in colourless prisms, m. p. 107—108°, soluble in hot water, insoluble in sodium hydrogen carbonate solution. Analysis indicated that dehydration as well as benzoylation had occurred, and the product was probably 3-*benzoyldihydro-4-oxo-5* : 5-*pentamethyleneglyoxaline* (Found: C, 70·5; H, 6·25; N, 10·9. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·25; N, 10·9%).

*Preparation of Some New Thiohydantoin Derivatives.*—New *N*- and *S*-methyl derivatives of 5 : 5-disubstituted thiohydantoins required as intermediates were prepared by application of methods described in Part III (Carrington and Waring, *J.*, 1950, 354) to the appropriate thiohydantoins. Their structures were proved by reasoning similar to that described there.

5-Methyl-5-phenyl-2 : 4-dithiohydantoin (Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090) was treated with aqueous 2-aminoethanol and formed 4-2′-*hydroxyethylimino-5-methyl-5-phenyl-2-thiohydantoin*, colourless needles, m. p. 200—201° (75%) (Found: N, 17·0. $C_{12}H_{15}ON_3S$ requires N, 16·9%). This product on acid hydrolysis gave 5-methyl-5-phenyl-2-thiohydantoin (I; RR = Ph, Me), colourless needles (from aqueous methanol), m. p. 188—189° (73%) (Found: C, 57·9; H, 5·1; N, 13·6. Calc. for $C_{10}H_{10}ON_2S$: C, 58·25; H, 4·85; N, 13·6%). This compound had previously been reported (D.R.-P. 310,427; "Friedländer," Vol. XIII, p. 806) as having m. p. 169°. 5-Methyl-5-phenyl-2 : 4-dithiohydantoin with methyl sulphate gave 4 : 5-*dihydro-5-methyl-2-methylthio-5-phenyl-4-thioglyoxaline*, bright yellow needles (from aqueous methanol), m. p. 153° (24%) (Found: C, 55·9; H, 5·3; N, 11·7. $C_{11}H_{12}N_2S_2$ requires C, 55·9; H, 5·1; N, 11·9%), which on acid hydrolysis gave 5-*methyl-5-phenyl-4-thiohydantoin*, pale yellow prisms (from methanol), m. p. 238° (66%) (Found: C, 58·0; H, 5·0; N, 13·2. $C_{10}H_{10}ON_2S$ requires C, 58·25; H, 4·85; N, 13·6%). 3 : 5-Dimethyl-5-phenylhydantoin (Swiss P. 176,827 : *Chem. Abs.*, 1936, **30**, 248) and phosphorus pentasulphide, heated in decalin, formed 3 : 5-*dimethyl-5-phenyl-2* : 4-*dithiohydantoin*, yellow prisms (from methanol), m. p. 131—132° (48%) (Found: C, 56·2; H, 5·1; N, 11·7; S, 27·2. $C_{11}H_{12}N_2S_2$ requires C, 55·9; H, 5·1; N, 11·9; S, 27·1%). 3 : 5-Dimethyl-5-phenyl-2 : 4-dithiohydantoin with methyl iodide gave 2 : 5-*dihydro-3* : 5-*dimethyl-2-methylthio-5-phenyl-4-thioglyoxaline*, colourless needles (from methanol), m. p. 90—91° (86%) (Found: C, 57·4; H, 5·6; N, 11·0. $C_{12}H_{14}N_2S_2$ requires C, 57·6; H. 5·6; N, 11·2%), which on acid hydrolysis gave 3 : 5-*dimethyl-5-phenyl-4-thiohydantoin*, yellow needles (from aqueous methanol), m. p. 129—130° (65%) (Found: C, 59·9; H, 5·5; N, 12·9. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·45; N, 12·7%). 1 : 5-Dimethyl-5-phenylhydantoin (Long, Miller, and Troutman, *J. Amer. Chem. Soc.*, 1948, **70**, 902) and phosphorus pentasulphide, heated in decalin, gave 1 : 5-*dimethyl-5-phenyl-2* : 4-*dithiohydantoin*, pale yellow needles (from methanol), m. p. 194—195° (38%) (Found: C, 56·0; H, 5·5; N, 11·8. $C_{11}H_{12}N_2S_2$ requires C, 55·9; H, 5·1; N, 11·9%). 1 : 5-Dimethyl-5-phenyl-2 : 4-dithiohydantoin was treated with aqueous 2-aminoethanol and formed 4-2′-*hydroxyethylimino-1* : 5-*dimethyl-5-phenyl-2-thiohydantoin*, colourless needles (from methanol), m. p. 222—223° (94%) (Found: C, 59·2; H, 6·5; N, 15·7. $C_{13}H_{17}ON_3S$ requires C, 59·3; H, 6·5; N, 16·0%), which on acid hydrolysis gave 1 : 5-*dimethyl-5-phenyl-2-thiohydantoin* (VI; RR = Ph, Me), colourless prisms (from methanol), m. p. 196—197° (Found: C, 60·1; H, 5·4; N, 12·7. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·45; N, 12·7%). 1 : 5-Dimethyl-5-phenyl-2-thiohydantoin with diazomethane gave 1 : 3 : 5-*trimethyl-5-phenyl-2-thiohydantoin*, colourless needles (from methanol), m. p. 112° (25%) (Found: C, 61·5; H, 5·8; N, 11·5. $C_{12}H_{14}ON_2S$ requires C,

61·55; H, 6·0; N, 12·0%). 5-Methyl-5-phenyl-2-thiohydantoin with diazomethane yielded 3 : 5-*dimethyl-5-phenyl-2-thiohydantoin*, colourless prisms (from ethanol), m. p. 223—224° (38%) (Found : C, 59·9; H, 5·6; N, 12·2. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·45; N, 12·7%).

5-Ethyl-5-phenyl-2 : 4-dithiohydantoin (Henze and Smith, *ibid.*, 1943, **65**, 1090) was treated with aqueous 2-aminoethanol and formed 5-*ethyl*-4-2′-*hydroxyethylimino-5-phenyl-2-thiohydantoin*, colourless prisms (from water), m. p. 184—185° (64%) (Found : C, 59·1; H, 6·4; N, 15·7. $C_{13}H_{17}ON_3S$ requires C, 59·3; H, 6·5; N, 16·0%), which on acid hydrolysis gave 5-*ethyl-5-phenyl-2-thiohydantoin*, colourless prisms (from aqueous methanol), m. p. 171° (Found: C, 60·0; H, 5·4; N, 12·3. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·5; N, 12·7%).

5 : 5-Tetramethylene-2 : 4-dithiohydantoin (Carrington, *J.*, 1947, 681), heated with 2-aminoethanol, gave the corresponding 4-2′-hydroxyethylimino-derivative m. p. 232°, which on acid hydrolysis was converted into 5 : 5-*tetramethylene-2-thiohydantoin*, colourless prisms (from water), m. p. 197—198° (Found : N, 16·4; S, 19·2. $C_7H_{10}ON_2S$ requires N, 16·4; S, 18·8%) (66% overall yield).

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## 619. *Triterpenoids. Part XIV.* The Constitution of Quinovic Acid.*

By D. H. R. BARTON and P. DE MAYO.

On the basis of published evidence two formulæ are possible for quinovic acid. By stepwise degradational experiments a distinction between the two possibilities has been made. A new formulation for novic acid is advanced and justified by chemical and physical evidence.

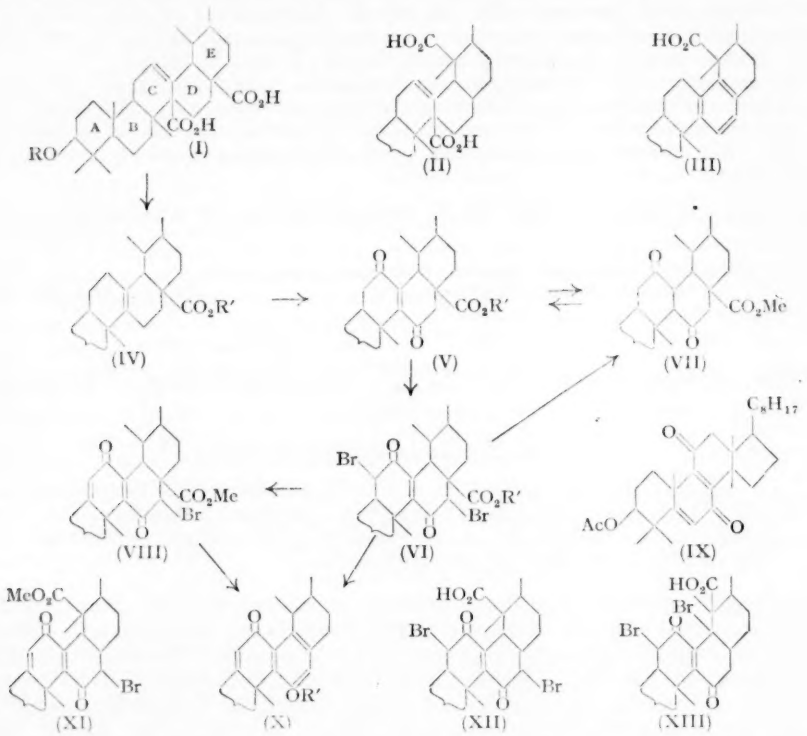
QUINOVIC ACID, a triterpenoid hydroxy-dicarboxylic acid present in cinchona bark and in the leaves and bark of several *Mitragyna* species (Badger, Cook, and Ongley, *J.*, 1950, 867), has been the subject of extensive investigations by the schools of Wieland and of Ruzicka (for summaries see Elsevier's " Encyclopaedia of Organic Chemistry," Vol. XIV, pp. 580, 1102 *et seq.*). The work has been crowned by Jeger's proposal (" Fortschritte der Chemie der organischen Naturstoffe," Springer-Verlag, 1950, Vol. VII, p. 69; Brossi, Bischof, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 244) of formula (I; R = H) for quinovic acid.

Whilst this formula provides in most respects an excellent representation of the chemistry of quinovic acid, it seemed to us that the published literature made (II; R = H), which also obeys the isoprene rule, equally admissible. Thus the evidence of Schmitt and Wieland (*Annalen*, 1945/1947, **557**, 1) proves that the carboxyl group which is *not* eliminated easily is in the $\gamma$-position with respect to the more substituted end of the double bond. It does not, however, distinguish between (I; R = H) and (II; R = H) for quinovic acid. Indeed the latter would provide a better explanation for the formation of the aromatic pyroquinovatrienic acid [which would then be represented by (III; R = H)]. It was the main objective of the experiments described in the present paper to secure a distinction between the two formulæ.

As a $\beta\gamma$-unsaturated acid quinovic acid readily loses carbon dioxide on melting and affords, with double-bond shift (see Barton and Brooks, *J.*, 1951, 257; Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457), pyroquinovic acid (IV; R = R′ = H). Oxidation of methyl pyroquinovate acetate (IV; R = Ac, R′ = Me) afforded methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me) (Wieland, Hartmann, and Dietrich, *Annalen*, 1936, **522**, 191). On treatment with bromine in acetic acid (V; R = Ac, R′ = Me) furnished a dibromo-derivative (cf. Wieland and Kraus, *Annalen*, 1932, **497**, 140)

* Part XIII, *J.*, 1953, 2178.

which, on the basis of its further reactions, must be formulated as (VI; R = Ac, R′ = Me). That bromination was not attended with rearrangement was shown as follows. Reduction of (V; R = Ac, R′ = Me) with zinc dust in acetic acid gave the saturated 1 : 4-dione (VII; R = Ac). Interestingly, the latter was re-oxidised to (V; R = Ac, R′ = Me) simply by boiling 5% methanolic potassium hydroxide (followed by remethylation and




reacetylation). Similar reduction and reoxidation of (VI; R = Ac, R′ = Me) likewise afforded (V; R = Ac, R′ = Me).

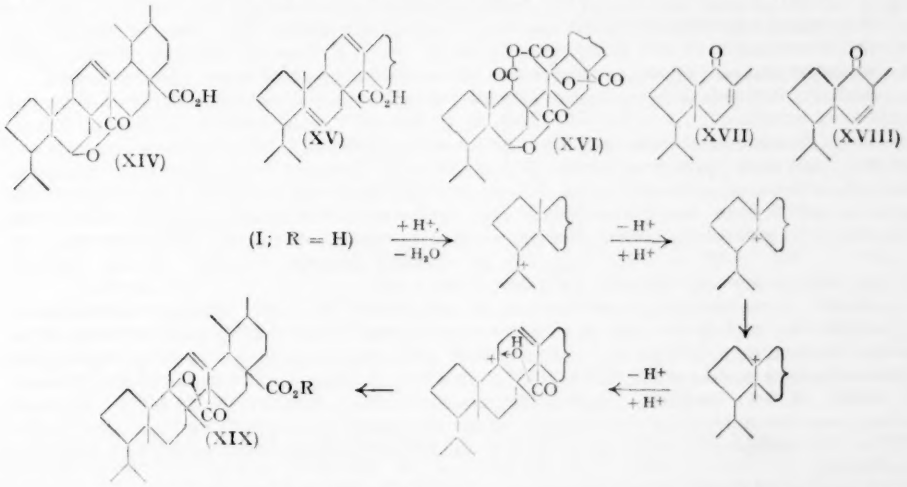
Treatment of the dibromo-ester (VI; R = Ac, R′ = Me) with silver nitrate and pyridine at room temperature (compare Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80; Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334) gave in good yield methyl monobromodiketopyroquinovadienoate acetate (VIII; R = Ac). The constitution assigned to the latter is based on the following considerations. (*a*) The ultra-violet absorption spectrum showed a maximum at 272 mμ corresponding in both position and intensity with that recorded for 7 : 11-diketolanosta-5 : 8-dienyl acetate (IX) (Voser, Montavon, Günthard, Jeger and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893). (*b*) The infra-red spectrum showed bands at 1736, 1277, and 1240 (tertiary $CO_2Me$ and acetate), 1692 (·CHBr·CO·C:C), and 1650 cm.$^{-1}$ (·C:C·CO·C:C·). The appropriate corresponding bands are also shown by (IX) (Voser *et al.*, *loc. cit.*).

The mono-bromo-compound (VIII; R = Ac) was also obtained readily by refluxing (VI; R = Ac, R′ = Me) with collidine or pyridine. On further treatment with these reagents (VIII; R = Ac) was recovered unchanged. However, when heated with collidine at 210° in a sealed tube, both (VI; R = Ac, R′ = Me) and (VIII; R = Ac) were smoothly converted into the phenol (X; R = Ac, R′ = H), further characterised as the diacetate (X; R = R′ = Ac). The constitution assigned to the phenol is supported by the ultra-

violet spectrum taken in both neutral and alkaline solution (see Experimental section) and by the infra-red spectrum which showed bands at 1730 and 1242 (acetate), and 1648 cm.$^{-1}$ (·C:C·CO·C:C·). In comparison the analogous *m*-hydroxyacetophenone showed a carbonyl maximum at 1688 cm.$^{-1}$. The shift to 1648 cm.$^{-1}$ in the phenol (X; R = Ac, R′ = H) demonstrates the conjugating effect of the extra ethylenic double bond.

The resistance of (VIII; R = Ac) to dehydrobromination, except under forcing conditions which involve concomitant decarbomethoxylation, is explained much better by that formula [based on (I; R = Ac)] than by the alternative (XI; R = Ac) [based on (II; R = Ac)]. Even more decisive evidence was obtained in the following way. Alkaline hydrolysis of methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me), followed by reacetylation, afforded the known acetate acid (V; R = Ac, R′ = H) (Wieland and Hoshino, *Annalen*, 1930, **479**, 179). That stereoisomerisation was not induced by the alkaline conditions was confirmed by remethylation to the parent ester (V; R = Ac, R′ = Me). Bromination of the acetate acid (V; R = Ac, R′ = H) under the conditions used for the methyl ester gave a dibromo-acid (VI; R = Ac, R′ = H), the constitution of which was proved by remethylation to the above-mentioned dibromo-ester (VI; R = Ac, R′ = Me). Treatment of the dibromo-acid with silver nitrate in pyridine solution at room temperature furnished the phenol (X; R = Ac, R′ = H). The smooth elimination of carbon dioxide in this reaction is explained by the β-bromo-acid formulation of (VI; R = Ac, R′ = H). It would find no explanation on the basis of formula (XII; R = Ac), itself derived from (II; R = Ac). A variant formula (XIII; R = Ac) for the dibromo-acid, based on (II; R = Ac), would explain the ease of decarboxylation, but the product of reaction would not be a phenol. On the basis of all this evidence we regard formula (I; R = H) for quinovic acid as substantiated.

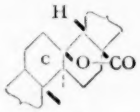
On treatment with strongly acidic reagents, quinovic acid affords, with loss of water, novic acid. Jeger (*loc. cit.*) has formulated the latter as (XIV). It seemed to us that this formula was somewhat improbable for the following reasons. (*a*) It involves a very stable δ-lactone ring. (*b*) The latter is postulated as being formed by non-Markownikoff addition to (XV). (*c*) The formula does not explain why the acid anhydride, which would be (XVI) on the



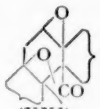

basis of (XIV), of the dicarboxylic acid derived from novaquinone gives two *ketones* [now formulated as (XVII) and (XVIII)] on pyrolysis. We took the view that, granted the accuracy of the expression (I; R = H) for quinovic acid, novic acid would be better regarded as the γ-lactone (XIX), formed from (I; R = H) by the mechanism indicated.

The accuracy of the expression (XIX; R = H) for novic acid has been justified in the following way. In the infra-red novic acid shows a somewhat displaced γ-lactone band at

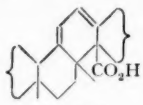
1766 cm.$^{-1}$ as well as the unconjugated carboxylic acid band at 1694 cm.$^{-1}$. In comparison oleanolic acid lactone (XX; R = H) (Barton and Holness, *J.*, 1952, 78) showed a $\gamma$-lactone band at 1774 cm.$^{-1}$, and 18-*iso*oleanolic lactone acetate bands at 1732 and 1240 (acetate) and 1770 cm.$^{-1}$ ($\gamma$-lactone). The displacement of the $\gamma$-lactone band of novic acid from its usual position is to be attributed to the double bond, for when the latter was saturated by conversion of methyl novate (XIX; R = Me) into methyl novate oxide (XXI; R = Me) the latter showed bands at 1732 and 1236 (acetate) and 1772 cm.$^{-1}$, the last being a clear indication of a $\gamma$-lactone grouping. Wieland and Erlenbach (*loc. cit.*) observed that when novic acid was heated with methanolic potassium hydroxide it was isomerised to a dicarboxylic acid designated " anhydroquinovic acid," from which it was regenerated by treatment with zinc chloride in acetic acid (Wieland and Utzino, *Annalen*, 1931, **488**, 242). On the basis of Jeger's novic acid formula, " anhydroquinovic acid " must be (XV); on the basis of (XIX; R = H) it must be the conjugated homoannular diene (XXII). We have found that, in agreement with (XXII), " anhydroquinovic acid " has $\lambda_{max.}$ 294 m$\mu$ ($\varepsilon$ = 6000). Its strongly positive rotation ($[\alpha]_D$ +310°) is also in agreement with its formulation as a pentacyclic triterpenoid in which ring C is diunsaturated. On pyrolysis Wieland and Erlenbach (*loc. cit.*) showed that, like other $\beta\gamma$-unsaturated acids, " anhydroquinovic acid " was readily decarboxylated to " pyroanhydroquinovic acid." Following the discussion by Barton and Brooks (*J.*, 1951, 278) of pyrolysis of



(XX)



(XXI)



(XXII)

similar dienic acids we would predict that the latter acid should not be a conjugated diene. This has been confirmed. Other aspects of novic acid chemistry are readily explained by (XIX; R = H) and do not call for further comment here.

## Experimental

For general experimental details see Part VII (*J.*, 1952, 2339). The infra-red spectra were kindly determined in carbon disulphide solution by Dr. J. E. Page and his staff (Messrs. Glaxo Laboratories Ltd.). $[\alpha]_D$ are in chloroform; ultra-violet absorption spectra are in ethanol.

*Methyl Dibromodiketopyroquinovate Acetate* (VI; R = Ac, R′ = Me).—Methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me), m. p. 219—221°, $[\alpha]_D$ +30° (*c*, 1·96), $\lambda_{max.}$ 270 m$\mu$ ($\varepsilon$ 7900) (Wieland, Hartmann, and Dietrich, *Annalen*, 1936, **522**, 191) (144 mg.) in acetic acid (9 ml.) containing hydrogen bromide (3 drops of 50% hydrogen bromide in acetic acid) was treated with bromine in acetic acid (10 ml., containing 18 mg. of bromine per ml.) and the solution left at room temperature in the dark for 4 days. The product was crystallised from methanol, to give *methyl dibromodiketopyroquinovate acetate*, m. p. 212—213° (decomp.), $[\alpha]_D$ +51° (*c*, 1·83), +52° (*c*, 1·84), $\lambda_{max.}$ 273 m$\mu$ ($\varepsilon$ 8600) (Found : C, 55·9; H, 6·4; Br 23·3. $C_{32}H_{44}O_6Br_2$ requires C, 56·1; H, 6·45; Br, 23·4%).

*Methyl Bromodiketopyroquinovadienoate Acetate* (VIII; R = Ac).—Methyl dibromodiketopyroquinovate acetate (50 mg.) in pyridine–silver nitrate (5 ml.; 20%) was left overnight at room temperature. The product, recrystallised from methanol, gave *methyl bromodiketopyroquinovadienoate acetate*, m. p. 226—228°, $[\alpha]_D$ −62° (*c*, 1·28), $\lambda_{max.}$ 272 m$\mu$ ($\varepsilon$ 12,800) (Found : C, 63·65; H, 7·1; Br 13·25. $C_{32}H_{43}O_6Br$ requires C, 63·7; H, 7·2; Br, 13·25%). This substance was also obtained by refluxing the parent dibromo-compound (100 mg.) with dry pyridine (13 ml.) or collidine (10 ml.) for 16 hr. and identified by m. p., mixed m. p., and absorption spectrum.

*Treatment of Methyl Dibromodiketopyroquinovate Acetate with Collidine.*—The dibromo-ester (70 mg.) in collidine (2 ml.) was heated in nitrogen in a sealed tube at 210° for 12 hr. The product, crystallised from methanol, gave the *phenol* (X; R = Ac, R′ = H) (40 mg.), m. p. 330—335° (decomp.), $[\alpha]_D$ +31° (*c*, 1·23), $\lambda_{max.}$ 344, 283, 253 m$\mu$ ($\varepsilon$ 4300, 8200, and 18,800, respectively), $\lambda_{inflex.}$ 227 ($\varepsilon$ 17,100), in 0·2N-ethanolic potassium hydride : $\lambda_{max.}$ 280, 247 m$\mu$ ($\varepsilon$ 9800 and 21,600 respectively) (Found : C, 77·7; H, 8·8. $C_{30}H_{40}O_4$ requires C, 77·55; H, 8·7%). The same compound, identified by m. p., mixed m. p. and absorption spectrum, was also

obtained smoothly by heating methyl monobromodiketopyroquinovadienoate acetate in collidine in the same way. It was also prepared, although in poor yield, by heating the dibromo-ester with pyridine in a sealed tube for 6 hr. at 150°. The phenol (X; R = Ac, R′ = H), was further characterised by heating it on the steam-bath with acetic anhydride and pyridine for 0·5 hr. This furnished the *acetate* (X; R = R′ = Ac), m. p. (from methanol) 190—191·5°, $[\alpha]_D$ +27° (*c*, 1·42), $\lambda_{max.}$ 257, 275, and 312 mμ (ε 12,600, 11,700, and 4500 respectively) (Found: C, 75·3; H, 8·1. $C_{32}H_{42}O_5$ requires C, 75·85; H, 8·35%).

*Bromination of Diketopyroquinovic Acid Acetate* (V; R = Ac, R′ = H).—Diketopyroquinovic acid acetate, m. p. 286—288° (Wieland and Hoshino, *Annalen*, 1930, **479**, 179) was prepared by alkaline hydrolysis (refluxing 10% ethanolic potassium hydroxide for 1 hr.) of the methyl ester acetate followed by re-acetylation. On treatment with diazomethane it refurnished the parent methyl diketopyroquinovate acetate, m. p. and mixed m. p. 218—220°, $[\alpha]_D$ +30° (*c*, 2·57).

Diketopyroquinovic acid acetate (100 mg.) in acetic acid (7 ml.) containing bromine (120 mg.) and hydrogen bromide (3 drops of 50% hydrogen bromide in acetic acid) was left at room temperature in the dark for 5 days. The acidic product, extracted with sodium carbonate solution, was very soluble in all solvents. It was characterised by methylation with diazomethane, to give methyl dibromodiketopyroquinovate acetate (57 mg.) (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +48° (*c*, 0·51)}. In a parallel experiment with 50 mg. of the diketo-acid acetate the acidic product was treated with silver nitrate and pyridine as above. The product gave the phenol (X; R = Ac, R′ = H) (20 mg.), identified by m. p., mixed m. p., and absorption spectrum.

Diketopyroquinovic acid acetate was recovered unchanged [confirmed by conversion into the methyl ester acetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +29° (*c*, 1·73)}] on treatment with hydrogen bromide in acetic acid as under the conditions of the bromination.

*Methyl Dihydrodiketopyroquinovate Acetate* (VII; R = Ac).—Methyl diketopyroquinovate acetate (200 mg.) in 10 ml. of 1 : 1 ether–methanol was shaken overnight at room temperature with zinc dust (1 g.), which had been activated by hot acetic acid and washed with methanol. The product afforded colourless *methyl dihydrodiketopyroquinovate acetate* (from methanol), m. p. 262—264°, $[\alpha]_D$ +47° (*c*, 1·71), with no high-intensity absorption in the ultra-violet (Found: C, 72·8; H, 9·2. $C_{32}H_{48}O_6$ requires, C, 72·7; H, 9·15%). This diketone (100 mg.) was refluxed with 5% methanolic potassium hydroxide (10 ml.) on the steam-bath for 2 hr. The product was methylated with diazomethane and reacetylated and crystallised from methanol, to give yellow methyl diketopyroquinovate acetate, identified by m. p. and absorption spectrum ($\lambda_{max.}$ 270 mμ; ε 7200).

When methyl dibromodiketopyroquinovate acetate (50 mg.) was similarly reduced and oxidised, methyl diketopyroquinovate acetate, identified by m. p., mixed m. p., and absorption spectrum, was likewise obtained.

*Methyl Novate Oxide* (XXI; R = Me).—Novic acid (Schmitt and Wieland, *Annalen*, 1945/47, **557**, 1) was converted into the methyl ester (Wieland and Erlenbach, *ibid.*, 1927, **453**, 83), m. p. 207—208°, $[\alpha]_D$ +132° (*c*, 0·52). The latter (100 mg.) in carbon tetrachloride (3 ml.) was treated with ozonised oxygen until it gave no colour with tetranitromethane. Crystallisation of the product from methanol gave *methyl novate oxide*, m. p. 246—247°, $[\alpha]_D$ +80° (*c*, 1·90) (Found: C, 74·6; H, 9·1. $C_{31}H_{46}O_5$ requires, C, 74·65; H, 9·3%).

*Anhydroquinovic Acid* (XXII).—Novic acid (200 mg.) was heated with methanolic 3N-potassium hydroxide (2 ml.) at 170° for 3 hr. (cf. Wieland and Erlenbach, *loc. cit.*). Recrystallisation of the product from acetic acid gave "anhydroquinovic acid," m. p. 222—224° (decomp.), $[\alpha]_D$ +310° (*c*, 0·25), $\lambda_{max.}$ 294 mμ (ε 6000). This (20 mg.) was pyrolysed *in vacuo* at 245° as described by Wieland and Erlenbach (*loc. cit.*). The product "pyroanhydroquinovic acid" had no selective absorption in the ultra-violet (at 220—350 mμ, ε <3000).

We are indebted to the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited, for financial support. One of us (P. de M.) thanks the Colonial Products Research Council for a Maintenance Grant. We are specially grateful to Professor J. W. Cook, F.R.S., and the N. V. Amsterdamsche Chinine Fabriek for supplies of quinovic acid. We also thank Dr. Mary Fieser for her interest in this problem.

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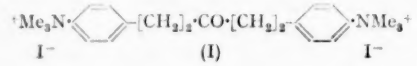
## 620. *Diacid Bases. Part I. Compounds related to 1 : 5-Diphenylpentane-pp'-bis(trialkylammonium) Salts as Anti-cholinesterases.*

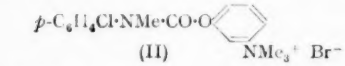
By F. C. Copp.

The discovery that 3-oxo-1 : 5-diphenylpentane-*pp*-bis(trimethylammonium) di-iodide was a selective inhibitor of true cholinesterase led to the preparation, by routine methods, of a number of related mono- and bisquaternary compounds derived from 1 : 5-diphenyl-pentane, -pentan-3-one, and -pentan-3-ol.

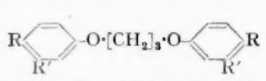
3-Oxo-1 : 5-diphenylpentane-*pp'*-bis(trimethylammonium) di-iodide (I), prepared in these laboratories by Dr. J. R. Catch and the present author, was found to possess marked anti-cholinesterase properties (Fulton and Mogey, personal communication), being much more effective against true than against pseudo-cholinesterase (for differentiation of true and pseudo-cholinesterases see Augustinsson, *Acta Physiol. Scand.*, 1948, **15**, Suppl. 52, p. 21). Further work was therefore undertaken on the relation of structure to activity in this series. Chemically, (I) differs from earlier selective inhibitors of true cholinesterase, *e.g.*, caffeine (Zeller and Bissegger, *Helv. Chim. Acta*, 1943, **26**, 1619), di-2-chloroethylmethylamine (Adams and Thompson, *Biochem. J.*, 1948, **42**, 170), and "Nu-1250" (II) (Hawkins and Mendel, *ibid.*, 1949, **44**, 260). Whilst this work was in progress the related compounds (III*a* and *b*) were reported by Funke and Depierre (*Compt. rend.*, 1950, **230**, 245) and by Funke, Krucker, and Depierre (*ibid.*, 1950, **231**, 498) to possess high anti-cholinesterase activity, much increased by the introduction of one or two dimethylcarbamoyloxy-groups, as in (IV) (*idem*, *ibid.*, 1952, **234**, 762).



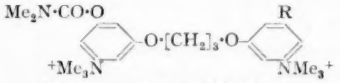
I⁻ (I) I⁻



(II)



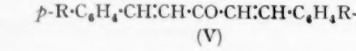
(III*a*; R = $NMe_3^+$, R' = H)
(III*b*; R = H, R' = $NMe_3^+$)



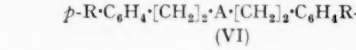
(IV; R = H or O·CO·$NMe_2$)

The starting material for (I) was 1 : 5-bis-*p*-dimethylaminophenylpentadien-3-one (V; R = $NMe_2$) (Sachs and Lewis, *Ber.*, 1902, **35**, 3576) which had been previously catalytically reduced to 1 : 5-bis-*p*-dimethylaminophenylpentan-3-one (VI; R = $NMe_2$, A = CO) (Rupe, Collin, and Schmiderer, *Helv. Chim. Acta*, 1931, **14**, 1340). In our hands, hydrogenation of (V; R = $NMe_2$) over freshly prepared Raney nickel (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471) gave solely 1 : 5-bis-*p*-dimethylaminophenylpentan-3-ol (VI; R = $NMe_2$, A = CH·OH), though use of Raney nickel which had been kept for 2—4 months led to (VI; R = $NMe_2$, A = CO); use of palladium–charcoal led to a mixture of the alcohol and ketone. With phenyl- or ethyl-magnesium bromide the ketone gave the alcohols (VI; R = $NMe_2$, A = CPh·OH) (Rupe, Collin, and Schmiderer, *loc. cit.*) and (VI; R = $NMe_2$, A = CEt·OH). Reduction of the ketone by Clemmensen's method was very slow but eventually gave (VI; R = $NMe_2$, A = $CH_2$). These bases were easily converted into the corresponding bisquaternary salts (Table 1, p. 3118) whilst a few monoquaternary salts were also prepared by similar methods (see Table 2).

The anti-cholinesterase properties of all these compounds were examined in the Biological Division of these laboratories by Mrs. Muriel Fulton and Dr. Mogey. High activity against true cholinesterase only, considered on a molar basis, was not found unless two quaternary groups were present, and (VI; A = CO, R = $\overset{+}{N}Me_2Pr$) was the most active of these bisquaternary compounds. Since this compound was also amongst the least active



(V)



(VI)

against pseudo-cholinesterase, it was decidedly superior to the original compound (I) as a

*selective* inhibitor of true cholinesterase. The selective effects of (VI; A = CO, R = $\overset{+}{N}Me_2 \cdot CH_2 \cdot CH{:}CH_2$) (" 284C51 ") have been further examined by Austin and Berry (*Biochem. J.*, 1953, **53**, ix).

## Experimental

**1 : 5-*Bis*-p-*dimethylaminophenylpentadien*-3-*one*.**—This compound was prepared by the method of Sachs and Lewis (*loc. cit.*) from *p*-dimethylaminobenzaldehyde and acetone. **1 : 5-*Bis*-p-*diethylaminophenylpentadien*-3-*one***, prepared by analogous means in 12% yield, crystallised from ethanol in bright orange plates, m. p. 168—169° (Found: C, 79·9; H, 8·7; N, 7·5. $C_{25}H_{32}ON_2$ requires C, 79·7; H, 8·6; N, 7·4%). 1-*p*-Dimethylaminophenyl-5-phenylpentadien-3-one was prepared by Borsche's method (*Annalen*, 1910, **375**, 177), and 1-*p*-dimethylaminophenyl-5-*p*-methoxyphenylpentadien-3-one by that of Pfeiffer, Angern, Baches, Fitz, Prahl, Rheinholdt, and Stoll (*ibid.*, 1925, **441**, 258).

*Reduction of* **1 : 5-*Bis*-p-*dimethylaminophenylpentadien*-3-*one*.**—A suspension of 1 : 5-bis-*p*-dimethylaminophenylpentadien-3-one (10 g.) in ethanol or ethyl acetate (100 ml.) was reduced under hydrogen at 10 atm. with 5 g. of catalyst (see below) until absorption became very slow. The catalyst and solvent were removed and the residue treated with 10% excess of semicarbazide acetate in methanol (20 ml.) for 1 hr. The resulting semicarbazone, recrystallised from ethanol, had m. p. 151—152°; the regenerated ketone crystallised in plates (from methanol), m. p. 82—83°. Rupe, Collin, and Schmiderer (*loc. cit.*) found m. p. 86—87°. Its *dihydrobromide*, crystallised from ethanol, had m. p. 186—187° (Found: C, 51·5; H, 6·5; N, 5·7. $C_{21}H_{30}ON_2Br_2$ requires C, 51·7; H, 6·2; N, 5·8%).

The methanolic filtrate from the crude semicarbazone was evaporated and water added to the residue. The resulting **1 : 5-*bis*-p-*dimethylaminophenylpentan*-3-*ol*** crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 75—76° (Found: C, 77·2; H, 9·1; N, 8·5. $C_{21}H_{30}ON_2$ requires C, 77·25; H, 9·3; N, 8·6%). Its *dihydrobromide* had m. p. 205—206° (from ethanol) (Found: C, 51·7; H, 6·6; N, 5·85. $C_{21}H_{32}ON_2Br_2$ requires C, 51·6; H, 6·6; N, 5·7%). Its *O-acetate* was an oil, b. p. 206—210°/1·5 × $10^{-4}$ mm. (Found: C, 74·45; H, 8·55. $C_{33}H_{32}O_2N_2$ requires C, 75·0; H, 8·7%); the *O*-benzoate was a gum which decomposed on attempted distillation though it was satisfactorily characterised as its dimethiodide (see Table 1).

When palladium–charcoal was used for the hydrogenation the ketone and alcohol were obtained in approximately equal quantities. Raney nickel which had been kept for 3—5 months gave little or none of the alcohol whilst Raney nickel used within one month of preparation gave no ketone. The total yield in each case was *ca.* 75%.

By similar methods were prepared: **1 : 5-*bis*-p-*diethylaminophenylpentan*-3-*one***, b. p. 210°/0·05 mm. (Found: C, 79·3; H, 9·6. $C_{25}H_{36}ON_2$ requires C, 78·9; H, 9·5%) [*semicarbazone*, m. p. 129° (from methanol) (Found: C, 71·3; H, 8·7; N, 16·3. $C_{26}H_{39}ON_5$ requires C, 71·4; H, 8·9; N, 16·0%); *dihydrobromide*, m. p. 160—161° (from ethanol–ethyl acetate) (Found: C, 55·6; H, 7·1; N, 5·25. $C_{25}H_{38}ON_2Br_2$ requires C, 55·3; H, 7·1; N, 5·2%)]; **1-p-*dimethylaminophenyl*-5-*phenylpentan*-3-*one***, m. p. 75° (from methanol) (Found: C, 81·1; H, 8·1. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2%) [*semicarbazone*, m. p. 140° (from ethanol) (Found: N, 16·3. $C_{20}H_{26}ON_4$ requires N, 16·6%)]; **1-p-*dimethylaminophenyl*-5-p-*methoxyphenylpentan*-3-*one***, b. p. 180—185°/0·03 mm., m. p. 39—41° (Found: N, 4·6. $C_{20}H_{25}O_2N$ requires N, 4·5%) [*semicarbazone*, m. p. 156° (from ethanol) (Found: N, 15·0. $C_{21}H_{28}O_2N_4$ requires N, 15·2%)]; **1 : 5-*bis*-p-*diethylaminophenylpentan*-3-*ol***, b. p. 224—228°/0·1 mm., m. p. 50—51° (Found: C, 78·85; H, 9·9; N, 7·2. $C_{25}H_{38}ON_2$ requires C, 78·5; H, 9·9; N, 7·3%) [*dihydrobromide*, m. p. 174·5—175·5° (from ethanol–ethyl acetate) (Found: C, 54·85; H, 7·3; N, 5·2. $C_{25}H_{40}ON_2Br_2$ requires C, 55·1; H, 7·4; N, 5·1%)]; **1-p-*dimethylaminophenyl*-5-p-*methoxyphenylpentan*-3-*ol***, b. p. 220°/0·03 mm., m. p. 60° (Found: C, 76·25; H, 8·4; N, 4·5. $C_{20}H_{27}O_2N$ requires C, 76·6; H, 8·7; N, 4·5%).

**1 : 5-*Bis*-p-*dimethylaminophenylpentane*.**—1 : 5-Bis-*p*-dimethylaminophenylpentan-3-one (5 g.) was reduced with amalgamated zinc (125 g.), hydrochloric acid (250 ml., diluted with 200 ml. of water), and acetic acid (25 ml.) for 60 hr., a further 125 g. of zinc being added after 30 hr. and hydrochloric acid (20 ml.) every 6 hr. The resulting thick suspension was decanted from the undissolved zinc and made just alkaline with concentrated sodium hydroxide solution. The thick precipitate was filtered, washed with water, and repeatedly extracted with boiling ethanol. The combined extracts were evaporated and the residual gum (3·5 g.) was treated with excess of semicarbazide acetate in boiling methanol (10 ml.) for 2 hr. The resulting mixture was cooled, filtered, and evaporated. The residue was distributed between water (20 ml.) and ether (50 ml.) and kept at 0° for 72 hr. The mixed liquids were decanted from a

small amount of semicarbazone, and the ethereal layer dried and evaporated. The residue, **1** : 5-*bis*-p-*dimethylaminophenylpentane* was a viscous liquid (2·0 g.), b. p. 208—210°/0·2 mm. (Found: C, 80·6; H, 9·5; N, 8·9. $C_{21}H_{30}N_2$ requires C, 81·2; H, 9·7; N, 9·0%). The *dihydrobromide* crystallised from *iso*propanol–ethyl acetate as needles, m. p. 186—187° (Found: C, 53·1; H, 6·8; N, 5·65. $C_{21}H_{32}N_2Br_2$ requires C, 53·4; H, 6·8; N, 5·9%).

TABLE 1. *Bisquaternary salts of* (VI).

| R | A | Acid radical (X) | M. p. | Solvent for crystn. | Formula | Found (%) N | Found (%) X | Reqd. (%) N | Reqd. (%) X | Loss on drying (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| $NMe_3$ ..... | $CH_2$ | I | 126—127° | EtOH | $C_{23}H_{36}N_2I_2$ | 4·4 | 42·4 | 4·7 | 42·7 | 4·1 |
| $NMe_3$ ..... | CO | I | 244 | MeOH | $C_{23}H_{34}ON_2I_2$ | 4·7 | 41·85 | 4·6 | 41·9 | — |
| $NMe_2Et$ ..... | CO | I | 198 | Aq. PrⁱOH | $C_{25}H_{38}ON_2I_2$ | — | 40·3 | — | 39·9 | 2·6 |
| $NMe_2Pr$ ..... | CO | I | 178—179 | EtOH | $C_{27}H_{42}ON_2I_2$ | — | 38·5 | — | 38·2 | — |
| | | Br | 191—192 | ,, | $C_{27}H_{42}ON_2Br_2$ | — | 28·1 | — | 28·0 | — |
| $NMe_2{\cdot}CH_2{\cdot}CH{:}CH_2$ | CO | I | 179—180 | MeOH–EtOAc | $C_{27}H_{38}ON_2I_2$ [a] | — | 38·4 | — | 38·4 | — |
| | | Br | 199—200 | EtOH | $C_{27}H_{38}ON_2Br_2$ | — | 28·4 | — | 28·2 | — |
| $NMe_2{\cdot}CH_2{\cdot}C{:}CH$ ... | CO | I | 102—103 | ,, | $C_{27}H_{34}ON_2I_2$ | — | 38·8 | — | 38·7 | 2·6 |
| | | Br | α-form, 161 | EtOH–EtOAc | $C_{27}H_{34}ON_2Br_2$ | — | 28·45 | — | 28·4 | — |
| | | | β-form, 89—90 | EtOH | ,, | — | 27·8 | — | ,, | 5·3 |
| $NMeEt_2$ ..... | CO | I | 88—90 | ,, | $C_{27}H_{42}ON_2I_2$ | — | 38·2 | — | 38·2 | 8·0 |
| $NMe_2Bu$ ..... | CO | I | 206—207 | MeOH | $C_{29}H_{46}ON_2I_2$ | — | 36·6 | — | 36·7 | — |
| | | Br | 194—195 | EtOH–EtOAc | $C_{29}H_{46}ON_2Br_2$ | — | 26·8 | — | 26·7 | — |
| $NMe_2{\cdot}CH_2Ph$ ..... | CO | Cl | 127—128 | BuOH | $C_{35}H_{42}ON_2Cl_2$ | — | 12·4 | — | 12·3 | 4·8 |
| $NMe_3$ ..... | CH·OH | I | 205—206 | EtOH | $C_{23}H_{36}ON_2I_2$ | 4·4 | 41·3 | 4·6 | 41·6 | — |
| $NMe_2Et$ ..... | CH·OH | I | 178—180 | ,, | $C_{25}H_{40}ON_2I_2$ [b] | 4·5 | — | 4·4 | — | — |
| $NMeEt_2$ ..... | CH·OH | I | 112—113 | EtOH–PrⁱOH | $C_{27}H_{44}ON_2I_2$ | — | 38·4 | — | 38·1 | — |
| $NMe_3$ ..... | CH·OAc | I | 127—129 | MeOH | $C_{25}H_{38}O_2N_2I_2$ [c] | 4·35 | — | 4·3 | — | 4·8 |
| $NMe_3$ ..... | CH·OBz | I | 137 | MeOH–EtOH | $C_{30}H_{40}O_2N_2I_2$ | — | 35·0 | — | 35·5 | 3·1 |
| $NMe_3$ ..... | CEt·OH | I | 81—82 | EtOH | $C_{25}H_{40}ON_2I_2$ | 4·5 | 39·9 | 4·4 | 39·8 | 6·1 |
| $NMe_3$ ..... | CPh·OH | I | 151—153 | MeOH–$Et_2O$ | $C_{29}H_{40}ON_2I_2$ | 4·1 | 36·9 | 4·1 | 37·0 | — |

[a] Found: C, 49·1; H, 5·8. Reqd.: C, 49·1; H, 5·8%. [b] Found: C, 47·1; H, 6·1. Reqd.: C, 47·0; H, 6·3%. [c] Found: C, 46·0; H, 5·8. Reqd.: C, 46·1; H, 5·9%.

TABLE 2. *Monoquaternary salts and miscellaneous bisquaternary salts,* $p$-R·$C_6H_4$·B·A·B·$C_6H_4$·$NMe_3^+$-$p$ $X^-$.

| R | B | A | X | M. p. | Solvent for crystn. | Formula | Found (%) N | Found (%) X | Reqd. (%) N | Reqd. (%) X |
|---|---|---|---|---|---|---|---|---|---|---|
| H ..... | CH:CH | CO | I | 174° | Aq. MeOH | $C_{20}H_{22}ONI$ | 3·5 | — | 3·3 | — |
| H ..... | CH:CH | CO | Cl | 169—170 | EtOH–$Et_2O$ | $C_{20}H_{22}ONCl$ | — | 10·8 | — | 10·75 |
| $^+NMe_3I^-$ | CH:CH | CO | I | 195 | $H_2O$ | $C_{23}H_{30}ON_2I_2$ | 4·6 | — | 4·6 | — |
| H ..... | $[CH_2]_2$ | CO | I | 183 | EtOH | $C_{20}H_{24}ONI$ | — | 30·2 | — | 30·0 |
| $NMe_2HI$ ... | $[CH_2]_2$ | CO | I | 203 | EtOH–MeOH | $C_{22}H_{32}ON_2I_2$ | 4·5 | — | 4·7 | — |
| OMe ..... | $[CH_2]_2$ | CO | I | 173—175 | EtOH | $C_{21}H_{28}O_2NI$ | 3·3 | 28·0 | 3·1 | 28·0 |
| OMe ..... | $[CH_2]_2$ | CH·OH | I | 131 | MeOH–$Et_2O$ | $C_{21}H_{30}O_2NI$ | 3·3 | 28·2 | 3·1 | 27·9 |

**1** : 5-*Bis*-p-*dimethylaminophenyl*-3-*ethylpentan*-3-*ol*.—**1** : 5-Bis-*p*-dimethylaminophenylpentan-3-one (6·0 g.) was treated with ethylmagnesium bromide [from ethyl bromide (7·5 g.) and magnesium (1·5 g.)]. The *product* was a gum, which was sublimed at 155°/0·001 mm., and subsequently crystallised (m. p. 40°) (Found: N, 8·0. $C_{23}H_{34}ON_2$ requires N, 7·9%).

*Quaternary Salts*.—These *salts* were prepared from the appropriate alkyl halide and tertiary amine in acetone or ethanol (see Tables 1 and 2). M. p.s refer to materials which have been dried for 24 hr. *in vacuo* at room temperature; analyses refer to materials dried at 100° *in vacuo*, further (usually small) losses of uncertain significance occurring which are quoted only when >2%.

I am indebted to Mr. A. Bennett and Mr. P. R. W. Baker for the analyses, to Mr. A. Brown for experimental assistance, and to Mrs. M. Fulton and Dr. G. Mogey for the biological results.

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## 621. *Stages in Oxidations of Organic Compounds by Potassium Permanganate. Part III.* A Kinetic Study of the Oxidation of Pinacol by Manganic Pyrophosphate.*

By Alan Y. Drummond and William A. Waters.

Initial-rate studies of the oxidation of pinacol by aqueous manganic pyrophosphate have enabled the mechanism of the reaction to be elucidated in detail. The oxidation proceeds in stages: (*a*) ternary manganic–pinacol–pyrophosphate complexes are rapidly and reversibly formed; (*b*) these complexes slowly break down by a one-electron transition to give manganous pyrophosphate, acetone, and an active organic free radical (probably 2-hydroxy-2-propyl) which (*c*) is rapidly oxidised by a further equivalent of manganic salt.

Mechanisms of glycol fission have been subjects of much controversial discussion in which the relative merits of (*a*) homolytic bond fission and (*b*) heterolytic decomposition of intermediate cyclic complexes have been argued (Criegee, Kraft, and Rank, *Annalen*, **1933**, **507**, 159; Criegee, *ibid.*, **1948**, **560**, 132: Waters, *Trans. Faraday Soc.*, **1946**, **42**, 184; *Nature*, **1946**, **158**, 380; *Discuss. Faraday Soc.*, **1947**, **2**, 212; Merz and Waters, *J.*, **1949**, S15; Slack and Waters, *J.*, **1949**, 594; Kharasch, Friedlander, and Urry, *J. Org. Chem.*, **1949**, **14**, 91; **1951**, **16**, 533; Duke, *J. Amer. Chem. Soc.*, **1947**, **69**, 2885, 3054; Rigby, *J.*, **1950**, 1907; Cordner and Pausacker, *J.*, **1953**, 102). However, so many different reagents can effect selective 1 : 2-glycol fission that the exact mechanism of the reaction may not be independent of the chemical nature of the oxidiser.

In connection with homolytic mechanisms for this reaction the selective oxidation of 1 : 2-glycols by the complex salt manganic pyrophosphate, to which we have already directed attention (*J.*, **1953**, **435**, 440), is of particular interest since it clearly involves one-electron transfers and does proceed with liberation of a transient organic free radical. We have therefore studied kinetically the oxidation of pinacol by this reagent and find that glycol fission by manganic complexes occurs in an exactly similar way to glycol fission by ceric complexes (Duke and Forist, *J. Amer. Chem. Soc.*, **1949**, **71**, 2790; Duke and Bremer, *ibid.*, **1951**, **73**, 5179).

Following Duke's scheme, the electronic changes which occur in the pinacol oxidation can be represented by equations:

$$(1)\qquad HO{\cdot}CMe_2{\cdot}CMe_2{\cdot}OH + Mn^{III} \xrightarrow{Slow} {\cdot}O{\cdot}CMe_2{\cdot}CMe_2{\cdot}OH + Mn^{II} + H^+$$

$$(2)\qquad {\cdot}O{\cdot}CMe_2{\cdot}CMe_2{\cdot}OH \xrightarrow{Fast} O{:}CMe_2 + {\cdot}CMe_2{\cdot}OH$$

$$(3)\qquad Mn^{III} + {\cdot}CMe_2{\cdot}OH \xrightarrow{Fast} Me_2C{:}O + Mn^{II} + H^+$$

The oxidation of pinacol by manganic pyrophosphate does give an organic free radical active enough both to catalyse vinyl polymerisation and to reduce mercuric chloride (*J.*, in the press), and this experimental evidence is strongly indicative of the liberation of the strongly reducing 2-hydroxy-2-propyl radical ·$CMe_2$·OH (Merz and Waters, *loc. cit.*; Mackinnon and Waters, *J.*, **1953**, 323). The alternative mechanism of equations 1, 4, and 5, resembling that postulated for the oxidations effected by hydroxyl radicals and by lead tetra-acetate (refs. above), would not be expected to give a radical intermediate of such marked reducing power since the (? alkyloxy-)radical oxidation products of tertiary alcohols are much weaker reducing agents than those of primary and secondary alcohols.

$$(4)\qquad Mn^{III} + {\cdot}O{\cdot}CMe_2{\cdot}CMe_2{\cdot}OH \longrightarrow {\cdot}O{\cdot}CMe_2{\cdot}CMe_2O{\cdot} + Mn^{II} + H^+$$

$$(5)\qquad {\cdot}O{\cdot}CMe_2{\cdot}CMe_2{\cdot}O{\cdot} \longrightarrow 2Me_2C{:}O$$

It has been shown that the radical intermediate, ·CHMe·OH, from the oxidation of ethanol by hydroxyl radicals combines with free oxygen at a rate comparable with that of its further oxidation by hydroxyl radicals or by ferric ions (Kolthoff and Medalia, *J. Amer. Chem. Soc.*, **1949**, **71**, 3784; Kolthoff, Medalia, and Raaen, *ibid.*, **1951**, **73**, 1733).

* Part II, *J.*, **1953**, 440.

The 2-hydroxy-2-propyl radical, $\cdot CMe_2 \cdot OH$, however does not appear to react rapidly with oxygen, for the rate of oxidation of pinacol by manganic pyrophosphate is not detectably affected by bubbling either oxygen or nitrogen through the slowly reacting mixture. Though reaction (3) must be very much faster than (1), its velocity is not comparable with that of reaction (6) which leads to vinyl polymerisation since, as Fig. 1 shows, the overall rate of disappearance of manganic salt is decreased by the addition of vinyl cyanide In theory, when reaction (6) completely supplants reaction (3), the rate of consumption of

(6) $$CH_2{:}CH \cdot CN + \cdot CMe_2 \cdot OH \longrightarrow HO \cdot CMe_2 \cdot CH_2 \cdot CH(CN) \cdot \longrightarrow \text{Polymer}$$

manganic salt should be halved, but in fact when high concentrations of vinyl cyanide are used the decrease of rate is more than this. We suggest that the polymer, when formed, may preferentially adsorb one of the reactants and so reduce abnormally its bulk concentration in the aqueous phase.

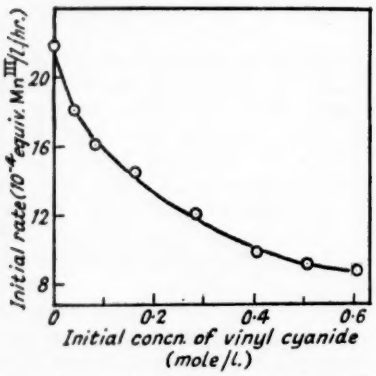



FIG. 1. *The effect of vinyl cyanide on the initial rate of oxidation of pinacol by manganic pyrophosphate.*

According to the simple reaction scheme of equations (1—3) the oxidation should be a process of the first-order with respect to both the manganic salt and the pinacol. As Table 1 shows, when pinacol is present in excess the initial rate of oxidation is always strictly of first order with respect to tervalent manganese. However, several plots of log

TABLE 1. *Reaction order with respect to manganic salt.* (Both pinacol and pyrophosphate are present in excess.)

(*a*) Initial pinacol, $7{\cdot}11 \times 10^{-2}$M. Temp., 45·0°. Pyrophosphate, 0·250M. Solution adjusted to pH 0·92.

| Initial $Mn^{III}$ ($10^{-2}$M) | Initial rate ($10^{-4}$ equiv. $Mn^{III}$/l./hr.) | $10^2 \times \frac{\text{Initial rate}}{\text{Initial concn.}}$ |
|---|---|---|
| 1·61 | 7·03 | 4·37 |
| 1·44 | 6·16 | 4·27 |
| 1·28 | 5·53 | 4·30 |
| 1·04 | 4·45 | 4·36 |
| 0·803 | 3·46 | 4·30 |

(*b*) Initial pinacol, $3{\cdot}28 \times 10^{-2}$M. Temp., 50·05°. Pyrophosphate, 0·305M. Solution adjusted to pH 0·75.

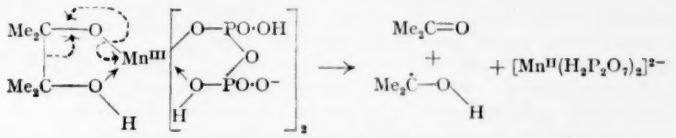
| Initial $Mn^{III}$ ($10^{-2}$M) | Initial rate ($10^{-4}$ equiv. $Mn^{III}$/l./hr.) | $10^2 \times \frac{\text{Initial rate}}{\text{Initial concn.}}$ |
|---|---|---|
| 2·08 | 1·37 | 6·57 |
| 1·92 | 1·22 | 6·35 |
| 1·76 | 1·16 | 6·60 |
| 1·60 | 1·03 | 6·46 |
| 1·44 | 0·908 | 6·30 |
| 1·28 | 0·837 | 6·53 |
| 0·96 | 0·625 | 6·51 |
| 0·80 | 0·504 | 6·30 |

(initial rate) against log [pinacol] indicated that the reaction order with respect to pinacol was about 0·8. Hence equation (1), as written, does not fully represent the rate-determining step in the oxidation. Now Duke and his colleagues (*loc. cit.*) in their studies of the oxidation of butane-2 : 3-diol by ceric salts suggested that there was a rapid initial formation of an organometallic complex in which a molecule of the glycol reversibly displaced another group from co-ordination with cerium. Then, concluding that only the complexed glycol was oxidised, they showed that the apparent reaction order with respect to total glycol obviously became less than unity.

Since Watters and Kolthoff (*J. Amer. Chem. Soc.*, 1948, **70**, 2455) have shown that in the pH range with which we have been concerned manganic pyrophosphate exists mainly

as the complex anion $[Mn(H_2P_2O_7)_3]^{3-}$, the equilibrium for our system can be written as (7); corresponding equations can be formulated for the other pyrophosphate anions, *e.g.*, $H_3P_2O_7^-$, which are also concerned. The true oxidation must be ascribed to the slower breakdown of this complex to bivalent manganese and an organic free radical, perhaps by the route of equation (1), or perhaps (and we favour this view) by a relayed one-electron switch, combining equations (1) and (2), which immediately liberates the 2-hydroxy-2-propyl free radical, *e.g.* :

$$\text{Pinacol} + Mn(H_2P_2O_7)_3^{3-} \underset{K}{\rightleftharpoons} [Mn(\text{Pin.})(H_2P_2O_7)_2]^- + H_2P_2O_7^{2-}. \quad (7)$$




(The broken arrows show single-electron movements.)

Equation 7 leads to the relationships :

$$[\text{Complex}] = \frac{K.[\text{Pinacol}][\{Mn(H_2P_2O_7)_3\}^{3-}]}{[H_2P_2O_7^{2-}]} = K.[Mn^{III}]\left\{\frac{[\text{Pinacol}]}{[H_2P_2O_7^-] + K.[\text{Pinacol}]}\right\}$$

where [Complex] = concentration of manganic–pinacol–pyrophosphate ternary complex, [Pinacol] = concentration of *free* pinacol, and $[Mn^{III}]$ = total concentration of manganic compounds. If the breakdown of the ternary complex is the rate-determining stage then $-d[Mn^{III}]/dt = 2k_7[\text{Complex}]$, which represents a first-order reaction with respect to $Mn^{III}$.

Now it is known that pyrophosphate anions co-ordinate extremely strongly with $Mn^{III}$, and hence $K$ should be small. Since in most of our experiments pyrophosphate was used in large excess the value of $[H_2P_2O_7^{2-}]$ can be taken as constant in the rate equation which can then be written as :

$$\frac{1}{-d[Mn^{III}]/dt} = \frac{1}{2k_7[Mn^{III}]}\left(\frac{[H_2P_2O_7^{2-}]}{K.[\text{Pinacol}]} + 1\right)$$

In these circumstances, though [Pinacol] is not directly calculable it can, at the commencement of the reaction, only be slightly less than the total pinacol concentration, and, as expected, experimental plots of 1/(Initial rate) against 1/[Pinacol taken] were nearly linear. From the slopes $([H_2P_2O_7^{2-}]/2k_7K[Mn^{III}])$ and intercepts on the rate axis $(1/2k_7[Mn^{III}])$ of such graphs it has been possible to calculate an approximate value of $K/[H_2P_2O_7^{2-}]$ from which values of [Pinacol], *i.e.*, of *free* pinacol, could be deduced. These calculated values have been used in Fig. 2, in which lines *A* and *B* summarise the results of two series of experiments carried out at different temperatures and different acidities (see Experimental Section). The linearity of these graphs justifies the assumption of equation (7), that only *one* pinacol molecule has entered the ternary complex by replacing one bidentate pyrophosphate group.

When the initial concentration of the pinacol was increased and that of pyrophosphate decreased, so as to favour the formation of a complex containing more than one pinacol molecule, *e.g.*, $Mn(\text{Pinacol})_2(H_2P_2O_7)^+$, experimental deviations illustrated by line *C* of Fig. 2 were such as to indicate that complexes containing two or more pinacol groups decompose more rapidly than those containing but one. This is the reverse of the behaviour observed with the ceric–butane-2 : 3-diol complexes by Duke and Bremer (*loc. cit.*) and with manganic–oxalate complexes by Duke (*J. Amer. Chem. Soc.*, **1947**, **69**, 2885) and by Taube (*ibid.*, 1948, **70**, 1216). However, under our experimental conditions the manganic ion is very greatly stabilised by the strongly co-ordinating pyrophosphate group, displacement of which would tend to increase the chemical reactivity of the system. Equation (7) indicates that the formation of the reactive complex, and consequently the rate of oxidation, should be retarded by increasing the pyrophosphate concentration. Provided that conditions are so chosen that the equilibrium of equation (7) lies far to the left then the rate

of oxidation should, at constant pH, be inversely proportional to the free pyrophosphate concentration, and the data of Table 2 show that this is the case.

As mentioned in Part II (*J.*, 1953, 440), all oxidations effected by manganic pyrophosphate proceed considerably faster at higher acidities. For the pinacol oxidation the variation of the initial rate with hydrogen-ion concentration for two different concentrations of pyrophosphate is shown in Fig. 3. As would be expected, this relationship is not linear

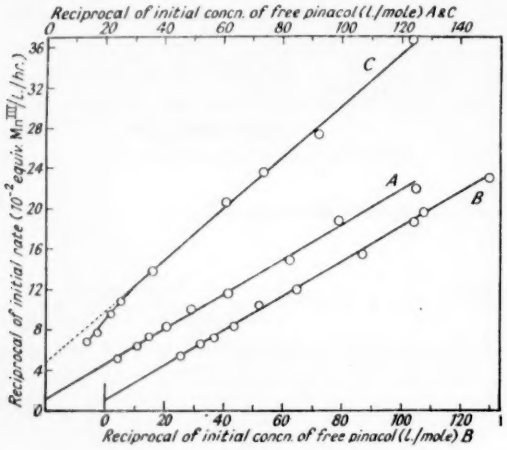



FIG. 2. *Calculated relationship between* 1/(*Oxidation rate*) *and* 1/[*Free pinacol*].

For concns., pH values, and temperatures of lines *A*, *B*, and *C* see the corresponding sections (*a*), (*b*), and (*c*) of Table 3 (p. 3123).

N.B. The zero position on the concentration axis for line *B* is different from that for lines *A* and *C*.

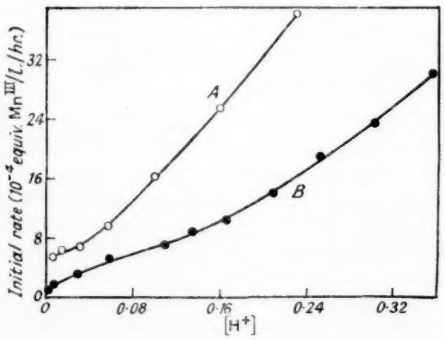



FIG. 3. *Dependence of initial rate of oxidation on acidity.*

Temp. = 35·0°. Initial concn. of pinacol = 5·80 × $10^{-2}$M.

*A*, 0·106M-Pyrophosphate. Initial $Mn^{3+}$ = 1·94 × $10^{-2}$M.

*B*, 0·159M-Pyrophosphate. Initial $Mn^{3+}$ = 1·86 × $10^{-2}$M.

The acidities were changed by addition of dilute sulphuric acid: for each reaction mixture the final acidity was measured by use of a pH-meter and glass electrode.

TABLE 2. *The dependence of rate upon the pyrophosphate concentration.*

Each solution contained initially 1·41 × $10^{-2}$M-manganic salt and 3·35 × $10^{-2}$M-pinacol. The pH was adjusted to 1·19 and the ionic strength was kept approximately constant by replacing acid and pyrophosphate by 0·305M-potassium chloride.

Temperature of reactions 35·0°.

The concentration of *free* pyrophosphate given below has been calculated by assuming that each manganic ion is complexed with 3 pyrophosphate groups.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Free pyrophosphate ($10^{-2}$M) ..... | 7·61 | 6·91 | 5·49 | 4·80 | 4·10 | 3·49 | 2·78 |
| Initial rate ($10^{-4}$ equiv. $Mn^{III}$/l./hr.) ... | 2·86 | 3·25 | 4·19 | 4·68 | 5·40 | 6·50 | 8·27 |
| $10^5$ Rate × [Pyrophosphate] ..... | 2·18 | 2·25 | 2·30 | 2·25 | 2·21 | 2·27 | 2·30 |

since equation (7) is but one representative of a whole series of equilibria involving free and complexed pyrophosphate anions, $H_3P_2O_7^-$, $H_2P_2O_7^{2-}$, etc., each of which is a weak acid. Watters and Kolthoff (*loc. cit.*) have shown that both the structure and the redox potential of manganic pyrophosphate are pH-dependent. Again, shifts in equilibria between complexed $H_3P_2O_7^-$ and $H_2P_2O_7^{2-}$ groups will undoubtedly change the ease with which a pinacol molecule can displace a pyrophosphate group in forming the ternary reaction complex, and the natural result of this is exemplified in the present work.

## Experimental

*Materials.*—Sodium manganic pyrophosphate solutions were prepared from "AnalaR" reagents as described in Part II (*loc. cit.*). Pinacol was crystallised 4 times from distilled water and was used as the dry hexahydrate, m. p. 46·7°. Vinyl cyanide was freed from stabiliser by washing it with N-sodium hydroxide and then water. After drying, it was distilled under a reduced pressure of nitrogen.

*Kinetic Measurements.*—The reactions were carried out in a thermostat regulated to within ±0·1°. After measured time intervals aliquot portions of mixtures were added to potassium iodide solutions, and the liberated iodine was titrated with standard sodium thiosulphate. pH adjustment was made with dilute sulphuric acid and, by use of a glass electrode, checked against standard buffers. In all cases titre–time plots were found to be linear for the first 7—10% of the reaction. The initial reaction velocities were measured from the slopes of these linear plots which always included 8—12 experimental points. Experiments in which vinyl cyanide was added were performed under nitrogen. Before mixing, the reactant solutions were blown out for 15 min. with a brisk stream of purified nitrogen, and during the reaction the mixtures were stirred rapidly whilst a slow stream of nitrogen was passed through them. When large amounts of polymer were formed the rate measurements were less accurate, since adsorption on the polymer tended to interfere with the iodine–thiosulphate end-point. In all other cases reactions carried out in a stream of oxygen took place at the same rates as those of comparable mixtures examined under nitrogen or air. The initial addition of manganous salts had no effect on the reaction velocity.

Table 3 gives the data from which the calculations for the construction of Fig. 2 have been made.

Table 3. *Dependence of the initial rate on the pinacol concentration.*

(*a*) Temp. 30·05°. pH 0·52. 0·165M-Pyrophosphate. Initial $Mn^{III} = 2·53 \times 10^{-2}$M.

| [Pinacol] (M × $10^3$) Total | Free (calc.) | Initial rate ($10^{-4}$ equiv. $Mn^{III}$/l./hr.) | $10^{-2}$/ Rate | 1/ [Pinacol] |
|---|---|---|---|---|
| 9·11 | 8·02 | 4·55 | 22·0 | 125 |
| 11·4 | 10·1 | 5·32 | 18·8 | 99 |
| 13·7 | 12·1 | 6·69 | 14·9 | 82·6 |
| 18·2 | 16·2 | 8·59 | 11·6 | 61·7 |
| 22·8 | 20·3 | 10·0 | 10·0 | 49·3 |
| 27·3 | 24·5 | 12·1 | 8·26 | 40·8 |
| 31·9 | 28·6 | 13·8 | 7·26 | 35·0 |
| 36·4 | 32·5 | 15·8 | 6·33 | 31·0 |
| 45·5 | 41·0 | 19·7 | 5·06 | 24·4 |

(*b*) Temp. 50·0°. pH 0·72. 0·387M-Pyrophosphate. Initial $Mn^{III} = 2·04 \times 10^{-2}$M.

| [Pinacol] (M × $10^3$) Total | Free (calc.) | Initial rate ($10^{-4}$ equiv. $Mn^{III}$/l./hr.) | $10^{-2}$/ Rate | 1/ [Pinacol] |
|---|---|---|---|---|
| 8·33 | 7·71 | 4·33 | 23·1 | 129·7 |
| 10·0 | 9·29 | 5·08 | 19·7 | 107 |
| 12·5 | 11·5 | 6·43 | 15·5 | 87 |
| 16·7 | 15·4 | 8·33 | 12·0 | 64·9 |
| 20·8 | 19·2 | 9·61 | 10·4 | 52·1 |
| 25·0 | 22·9 | 12·1 | 8·26 | 43·7 |
| 29·2 | 27·0 | 13·9 | 7·17 | 37·0 |
| 33·3 | 30·9 | 15·2 | 6·58 | 32·4 |
| 41·7 | 38·6 | 18·6 | 5·38 | 25·9 |

(*c*) Temp. 35·0°. pH 1·36. 0·107M-Pyrophosphate. Initial $Mn^{III} = 2·04 \times 10^{-2}$M.

| | | | | |
|---|---|---|---|---|
| 6·24 | 5·36 | 1·97 | 50·8 | 187 |
| 9·36 | 8·06 | 2·72 | 36·8 | 124 |
| 12·5 | 10·8 | 3·65 | 27·4 | 92·6 |
| 15·6 | 13·6 | 4·23 | 23·6 | 73·5 |
| 18·7 | 16·4 | 4·86 | 20·6 | 61·0 |
| 31·6 | 27·7 | 7·24 | 13·8 | 36·1 |
| 43·7 | 39·3 | 9·26 | 10·8 | 25·5 |
| 49·9 | 45·3 | 10·5 | 9·52 | 22·1 |
| 62·4 | 57·0 | 13·1 | 7·63 | 17·5 |
| 78·6 | 71·4 | 14·7 | 6·80 | 14·0 |

*Identification of Products.*—A stream of air was passed through the reaction mixture into saturated aqueous sodium hydrogen sulphite. The latter solution was then decomposed by dilute acid; water and volatile organic compounds were carried by a stream of air into a cold trap (carbon dioxide–ethanol). The collected solution gave positive indigo and nitroprusside reactions for the Me·CO· group (Feigl, "Spot Tests," Elsevier Publ. Co., 1947, pp. 349, 351). Identical treatment of solutions not oxidised by manganic salt gave no such reactions. Acetone is the only methyl ketone which could have been formed in these circumstances.

One of us (A. Y. D.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

The Dyson Perrins Laboratory, Oxford. [*Received, April 29th,* 1953.]

## 622. *Sesquiterpenoids. Part III.* The Stereochemistry of Caryophyllene.*

By A. Aebi, D. H. R. Barton, and A. S. Lindsey.

Mild acid-catalysed hydration of caryophyllene oxide affords a disecondary glycol formulated as 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]dodecane-2 : 9-diol. Similar hydration of *iso*caryophyllene oxide † furnishes a glycol stereoisomeric at $C_{(9)}$. These experiments prove that caryophyllene and *iso*caryophyllene are geometrical isomers about the endocyclic ethylenic linkage. On the basis of relative reactivities towards electrophilic reagents and by consideration of the course of isomerisation induced by nitrous acid, caryophyllene is regarded as the *trans*-isomer (I), and *iso*caryophyllene as the *cis*-isomer (X)

On palladium-catalysed hemihydrogenation both caryophyllene and *iso*caryophyllene give the same (*cis*-)dihydro-compound.

In recent communications (Šorm, Dolejš, and Pliva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 186; Barton and Lindsey, *Chem. and Ind.*, 1951, **313**; *J.*, 1951, 2988; Dawson, Ramage, and Wilson, *Chem. and Ind.*, 1951, 464; Barton, Bruun, and Lindsey, *ibid.*, 1951, 910; 1952, 691; *J.*, 1952, 2210; Dawson and Ramage, *J.*, 1951, 3382; Monteath Robertson and Todd, *Chem. and Ind.*, 1953, 437) the constitution (I) has been established for caryophyllene.† The *trans*-configuration for the ring fusion (cf. Rydon, *J.*, 1937, 1340) is demonstrated by the elegant *X*-ray studies of Robertson and Todd (*loc. cit.*). We now turn to two of the remaining problems of caryophyllene chemistry: the nature of *iso*caryophyllene and the configuration of the endocyclic ethylenic linkage.

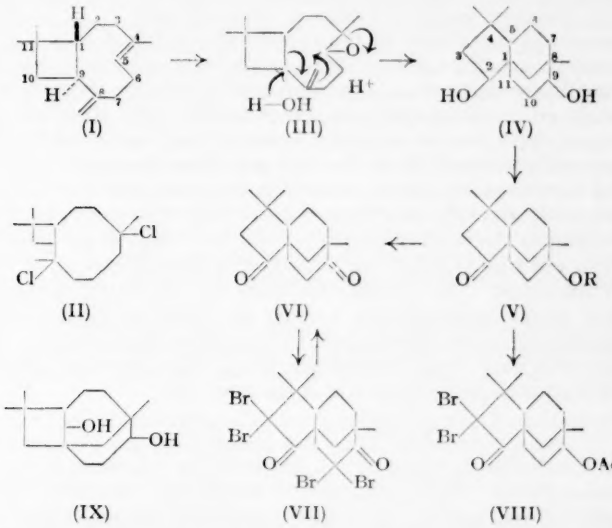
A close relation between caryophyllene and *iso*caryophyllene is indicated by the fact (see Simonsen and Barton, *op. cit.*) that both afford the same dihydrochloride (II). Caryophyllene and *iso*caryophyllene nitrosochlorides, on treatment with benzylamine, give the *same* nitrolbenzylamine. This would be best explained (see Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1952, 691) if the two nitrosochlorides were stereoisomers, *not* structural isomers. The same conclusion can be reached from the important work of Ramage and Simonsen (*J.*, 1938, 1208; see Barton, Bruun, and Lindsey, *loc. cit.*). In addition Ramage and Simonsen have demonstrated that the exocyclic methylene grouping ($>C{=}CH_2$) is retained in *iso*caryophyllene. The infra-red spectrum of *iso*caryophyllene shows bands at 3100, 1630, and 880 cm.$^{-1}$, confirming the retention of this structural feature. Bands at 1666, 828, and 834 cm.$^{-1}$, indicative of $-CH{=}CMe-$, are also present as in the spectrum of caryophyllene. On these grounds we advanced the view (Barton, Bruun, and Lindsey, *loc. cit.*) that caryophyllene and *iso*caryophyllene must have the same constitution and that, as described in the literature, *iso*caryophyllene must be either impure caryophyllene or a geometrical isomer of caryophyllene about the endocyclic ethylenic linkage. The first objective then was to establish the purity of *iso*caryophyllene. In agreement with previous workers (see Simonsen and Barton, *op. cit.*) we find that the rotation of *iso*caryophyllene ($\alpha_D$ −24°) is significantly different from that of caryophyllene ($\alpha_D$ −8 to −9°) and that *iso*caryophyllene does not afford a nitrosite. With perphthalic acid *iso*caryophyllene gave a crystalline oxide different from ordinary caryophyllene oxide (Treibs, *Chem. Ber.*, 1947, **80**, 56). Hydrogenation of this oxide furnished an oily dihydro-derivative which

* Part II, *J.*, 1952, 2210. The majority of the work reported in Part III has been summarised elsewhere (Aebi, Barton, and Lindsey, *Chem. and Ind.*, 1953, 487).

† We have used the name caryophyllene consistently for the naturally occurring hydrocarbon. Previous nomenclature (see Simonsen and Barton, "The Terpenes," Vol. III, Cambridge Univ. Press, 1952) distinguishes three (α-, β-, and γ-)caryophyllenes. The name α-caryophyllene has been replaced by humulene (see Simonsen and Barton, *op. cit.*). Since in the α- and β-caryophyllene alcohols the prefixes are not related to the prefixes used to name the hydrocarbons, it seems to us that a clarification of nomenclature results if the name "β-caryophyllene" is replaced by caryophyllene and the name "γ-caryophyllene" by *iso*caryophyllene. This is in fact, a reversion to the earlier nomenclature of Deussen and Lewinsohn (*Annalen*, 1907, **356**, 20). The work described in our present paper removes the main basis for doubts previously expressed as to the homogeneity of naturally occurring caryophyllene, in that it establishes a mechanism for the ready isomerisation of the latter to *iso*caryophyllene.

on acid-catalysed hydration gave a nicely crystalline α-glycol. Caryophyllene oxide, treated in the same way, afforded the known crystalline dihydro-derivative (Treibs, *loc. cit.*), which under the same hydration conditions gave only oils. Caryophyllene and *iso*caryophyllene are, therefore, different chemical individuals.

The nature of *iso*caryophyllene was decisively confirmed in the following way. Mild acid-catalysed hydration of ordinary caryophyllene oxide (III) (Barton and Lindsey, *J.*, 1951, 2988; Barton, Bruun, and Lindsey, *J.*, 1952, 2210) afforded in good yield a crystalline disecondary glycol, characterised as the diacetate. On the basis of the established structure of (III) and of reactions summarised in the sequel this glycol must be formulated as (IV). Oxidation by chromic acid proceeded in two stages. First, a keto-alcohol (V; R = H), characterised as the crystalline acetate (V; R = Ac) and as the 2 : 4-dinitrophenylhydrazone, was obtained. Secondly, a diketone (VI), characterised as the bis-2 : 4-dinitrophenylhydrazone, resulted. In the infra-red, (V; R = H) showed a band at 1730 cm.$^{-1}$ (five-ring ketone), and (VI) showed bands at 1732 (five-ring ketone) and 1702 cm.$^{-1}$ (six-ring ketone), in agreement with the structures assigned. Bromination of (VI) to completion gave a tetrabromo-diketone (VII), which regenerated (VI) on reduction with zinc dust and acetic acid. This shows that the two keto-groups of (VI) are flanked by




carbon atoms bearing at least four (replaceable) hydrogen atons. Bromination of (V; R = Ac) to completion gave a dibromo-acetate (VIII); therefore *both* keto-groups have two replaceable α-hydrogen atoms. A variant structure (IX) for the disecondary glycol is thus excluded. In agreement with the assigned structure, refluxing (VIII) with collidine provoked, not the elimination of hydrogen bromide, but reductive removal of one bromine atom. Wolff–Kishner reduction of the keto-alcohol (V; R = H) gave an oily alcohol oxidised by chromic acid to a ketone characterised as its 2 : 4-dinitrophenylhydrazone.

Similar hydration of *iso*caryophyllene oxide also afforded a crystalline disecondary glycol, shown to be a stereoisomer of (IV). Oxidation by chromic acid gave successively a keto-alcohol stereoisomeric with (V; R = H) and then the diketone (VI), already obtained from the glycol from ordinary caryophyllene oxide. The stereoisomer of (V; R = H) showed a band at 1730 cm.$^{-1}$ (five-ring ketone), thus confirming the assigned structure. The simplest interpretation of our experiments is that caryophyllene and *iso*caryophyllene oxides have identical configurations of the oxide ring at $C_{(4)}$ but differ in configuration at $C_{(5)}$. That *iso*caryophyllene is a geometrical isomer of caryophyllene is thus proved.

A decision has now to be made as to which of the structures (I) and (X) is caryophyllene and which is its stereoisomer. The phenyl azide reaction (Ziegler and Wilms, *Annalen*, 1950, **567**, 1; Blomquist, Liu, and Bohrer, *J. Amer. Chem. Soc.*, 1952, **74**, 3643) is not applicable since neither stereoisomer reacts. Prelog, Schenker, and Küng (*Helv. Chim. Acta*, 1953, **36**, 471) have shown that the strained *trans-cyclo*nonene reacts with per-acid faster than does the strain-free *cis-cyclo*nonene. A similar situation obtains in the *cyclo*decene series (Prelog, Schenker, and Günthard, *ibid.*, 1952, **35**, 1602). We find that caryophyllene reacts much faster with perphthalic acid than does *iso*caryophyllene. On this basis caryophyllene is the *trans*-isomer (I) and *iso*caryophyllene is the *cis*-isomer (X). The relative reactivities of the two isomers towards the electrophilic reagent nitrous acid (see above) are in agreement. These configurational assignments would also explain the modes of genesis of *iso*caryophyllene. The latter is obtained by steam-distillation of the mother-liquors from the preparation of caryophyllene nitrosite or by digestion of the nitrosite with alcohol. In the first method a derivative of *iso*caryophyllene does not appear to be an intermediate (see Experimental section) and the reaction can be regarded as the well-known isomerisation of a less stable to a more stable ethylenic linkage induced by nitrous acid. In the second method elimination of $NO_2^-$ and $NO^+$ from the nitrosite by reversal of the addition mechanism must generate nitrous acid, which then isomerises the less stable *trans*- to the more stable *cis*-isomer in the usual way.

Before the successful completion of the experiments outlined above an attempt had been made to decide the relative stability of the caryophyllenes by determining the relative stabilities of their dihydro-derivatives. Dihydro- and dihydro*iso*-caryophyllene, prepared by palladium-catalysed hemihydrogenation, were heated with naphthalene-β-sulphonic acid. In both cases there was no apparent isomerisation, as judged by the rotation,* whereas according to Ziegler and Wilms (*loc. cit.*) and Blomquist *et al.* (*loc. cit.*) the *trans*-compound should have afforded the *cis*-isomer. A comparison of the infra-red spectra of dihydro- and dihydro*iso*-caryophyllene then revealed that they were identical, apart from very minor differences in the relative intensities of a few bands in the finger-print region. The infra-red spectra of caryophyllene and *iso*caryophyllene, compared at the same time, revealed marked differences. We conclude therefore that isomerisation takes place on the palladium catalyst during hydrogenation, so that the dihydrocaryophyllene described in the literature (see Simonsen and Barton, *op. cit.*) is really dihydro*iso*caryophyllene (XI). In agreement with this view " dihydrocaryophyllene," dihydro*iso*caryophyllene, and *iso*-caryophyllene all react with perphthalic acid at the same rate.

(X) (XI)

The glycol (IV) has also been prepared by Atwater and Reid (personal communication from Dr. Evans B. Reid, Johns Hopkins University) by treatment of caryophyllene with performic acid, followed by alkaline hydrolysis. Thence the derived diketone (VI) was also obtained.

## Experimental

For general experimental directions see *J.*, 1952, 2339. Infra-red spectra, in carbon disulphide solution, were kindly determined by Dr. J. E. Page and his staff (of Messrs. Glaxo Laboratories Ltd.), using a Perkin–Elmer double-beam instrument. $[\alpha]_D$'s are in chloroform; ultra-violet absorption spectra are in ethanol unless specified to the contrary.

*Dihydroisocaryophyllene.*—Caryophyllene (for physical constants see Barton and Lindsey, *J.*, 1951, 2988) was hydrogenated according to the directions of Naves and Perrottet (*Helv. Chim. Acta*, 1941, **24**, 789). The " dihydrocaryophyllene " obtained had b. p. 96°/3 mm., $\alpha_D$ −29°. This hydrocarbon (5 g.) was heated with quinol (100 mg.) and naphthalene-β-sulphonic acid (100 mg.) in nitrogen at 150° (sealed tube) for 1½ hr. (cf. Blomquist, Liu, and Bohrer,

* The rotations of the dihydro-compounds described here, although not in perfect agreement, are more nearly identical than any of those reported previously (for summary see Naves and Perrottet, *Helv. Chim. Acta*, 1941, **24**, 789). The lack of agreement is doubtless due to the difficulty of carrying out a truly selective hemihydrogenation.

*J. Amer. Chem. Soc.*, 1952, **74**, 3643). The recovered hydrocarbon had b. p. 96°/3 mm., $\alpha_D$ −29° (l = 1).

Similar hydrogenation of *iso*caryophyllene afforded dihydro*iso*caryophyllene (XI), b. p. 96°/3 mm., $\alpha_D$ −31°. Treatment of this hydrocarbon with naphthalene-β-sulphonic acid as indicated above gave back a product, b. p. 96°/3 mm., $\alpha_D$ −33°.

*Hydration of Caryophyllene Oxide* (III).—The oxide (Treibs, *Chem. Ber.*, 1947, **80**, 56; Barton and Lindsey, *J.*, 1951, 2988) (10 g.) in a mixture of acetone (40 ml.), water (5 ml.), and 50% v/v sulphuric acid (2 ml.) was refluxed for 2 hr. on the steam-bath. The acetone was removed *in vacuo* and, after working up in the usual way, the product was crystallised from light petroleum (b. p. 80—100°), to give 4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*diol* (IV) (4·1 g.) as needles, m. p. 152—153°, $[\alpha]_D$ +5° (*c*, 1·9) (Found: C, 75·4; H, 11·2. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%). Experiments on the hydration of caryophyllene oxide with formic or hydrochloric acid in place of sulphuric acid gave lower yields of the same glycol. The yield was also lowered when the acetone was replaced by dioxan, or when the reaction was conducted at room temperature.

The glycol was acetylated with pyridine–acetic anhydride overnight at room temperature. Recrystallisation of the product from methanol gave the *diacetate* as prisms, m. p. 96—97°, $[\alpha]_D$ −54° (*c*, 2·05) (Found: C, 70·6; H, 9·0. $C_{19}H_{30}O_4$ requires C, 70·75; H, 9·4%).

*Chromic Acid Oxidation of* 4 : 4 : 8-*Trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*diol* (IV).—The glycol (1·0 g.) in "AnalaR" acetic acid was treated with chromium trioxide (550 mg.) in aqueous "AnalaR" acetic acid (10 ml., 80%) at room temperature and left overnight. Working up in the usual way (continuous ether-extraction) afforded an oil (900 mg.) which was chromatographed over alumina (14 fractions). Fractions 2—4, eluted with light petroleum (b. p. 40—60°), gave 4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*dione* (VI) (200 mg.). Recrystallised from light petroleum (b. p. 60—80°) as long needles this had m. p. 50—51°, $[\alpha]_D$ −109° (*c*, 1·9), $\lambda_{max.}$ 291—294 mμ, ε = 50 (Found: C, 77·2; H, 9·2. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·45%). Fractions 6—10, eluted with benzene, gave 4 : 4 : 8-*trimethyl*-2-*oxo*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecan*-9-*ol* (V; R = H) (450 mg.). Recrystallised from light petroleum (b. p. 60—80°) as needles, this had m. p. 84—85°, $[\alpha]_D$ +11° (*c*, 1·7) (Found: C, 76·4; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). A better yield of keto-alcohol was obtained in the following way. The glycol (1·0 g.) in "AnalaR" acetic acid (6 ml.) was treated with chromium trioxide (260 mg.) in aqueous acetic acid (20 ml.; 90%) at room temperature and left for 5 hr. Working up as above gave 400 mg. of pure keto-alcohol.

The diketone was characterised by conversion into the bis-2 : 4-*dinitrophenylhydrazone* in the usual way. Chromatographed in benzene solution over alumina and recrystallised from ethyl acetate–ethanol, this had m. p. 240—241° (Found: C, 54·1; H, 5·0. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1%).

The keto-alcohol was characterised by conversion into the 2 : 4-*dinitrophenylhydrazone*. Recrystallised from ethanol as needles, this had m. p. 179—180° (Found: C, 61·1; H, 7·05; N, 13·7. $C_{21}H_{28}O_5N_4$ requires C, 60·6; H, 6·8; N, 13·5%). Acetylation of the keto-alcohol with pyridine–acetic anhydride overnight at room temperature afforded the *acetate* (V; R = Ac). Purification by chromatography in benzene solution over alumina and recrystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 76—77°, $[\alpha]_D$ −34° (*c*, 1·35) (Found: C, 72·65; H, 9·4. $C_{17}H_{26}O_3$ requires C, 73·35; H, 9·4%). The keto-alcohol (100 mg.) in "AnalaR" acetic acid (2 ml.) was treated with chromium trioxide (50 mg.) in aqueous acetic acid (1 ml.; 80%) at room temperature and left for 2 days. The product was chromatographed over alumina [elution with light petroleum (b. p. 40—60°)], to give 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$] dodecane-2 : 9-dione (see above) (80 mg.), identified by m. p. and mixed m. p.

[With Dr. T. Bruun.] The keto-alcohol (100 mg.) in ethanol (1·5 ml.) containing dissolved sodium (56 mg.) was heated with hydrazine (1 ml.) at 180° overnight. The product was an oil. This was oxidised to the corresponding ketone by treatment with a slight excess of chromic acid in "AnalaR" acetic acid. The non-crystalline 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]-dodecan-9-one was characterised by conversion into the 2 : 4-*dinitrophenylhydrazone*, m. p. 190—191° (from chloroform–methanol), $\lambda_{max.}$ 369 mμ (in $CHCl_3$), ε = 20,500 (Found: N, 13·9. $C_{21}H_{28}O_4N_4$ requires N, 14·0%).

*Bromination of* 4 : 4 : 8-*Trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*dione* (VI).—The diketone (100·5 mg.) in "AnalaR" acetic acid (20 ml.) containing hydrogen bromide (1 drop of 50% hydrogen bromide in acetic acid) and twice the theoretical amount of bromine for the replacement of four α-hydrogen atom was left at room temperature in the dark for 48 hr. (uptake, determined by titration of an aliquot, 97·5%). There was no change in bromine uptake after

a further 7 days at room temperature. Working up and crystallisation of the product from ether afforded 3 : 3 : 10 : 10-*tetrabromo*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*dione* (VII) as colourless plates, m. p. 190—192°, $[\alpha]_D$ −68° (*c*, 1·9) (Found : C, 33·1; H, 3·5; Br, 58·3. $C_{15}H_{18}O_2Br_4$ requires C, 32·7; H, 3·3; Br, 58·2%). This compound resisted further bromination under the same conditions (no bromine uptake, confirmed by isolation). The tetrabromo-diketone (400 mg.) in " AnalaR " acetic acid (20 ml.) was refluxed with zinc dust (1 g.) for 4 hr. The product, crystallised from light petroleum (b. p. 40—60°), gave back the parent diketone (250 mg.), identified by m. p. and mixed m. p.

*Bromination of* 4 : 4 : 8-*Trimethyl*-2-*oxo*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodec*-9-*yl Acetate* (V; R = Ac).—The keto-acetate (see above) (30·3 mg.) was treated with bromine (4 Br) as for the diketone. After 50 hr. the uptake was 96·6% of the theoretical, unchanged after a further 7 days. Working up and crystallisation of the product from ether afforded 3 : 3-*dibromo*-4 : 4 : 8-*trimethyl*-2-*oxo*-tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodec*-9-*yl acetate* (VIII) as plates, m. p. 151—152°, $[\alpha]_D$ −14° (*c*, 0·9) (Found : C, 46·9; H, 5·3; Br, 36·5. $C_{17}H_{24}O_3Br_2$ requires, C, 46·7; H, 5·75. Br, 36·3%).

The dibromo-acetate (100 mg.) was refluxed with collidine (20 ml.; freshly redistilled) for 4 hr. Recrystallisation of the product from methanol gave 3-*bromo*-4 : 4 : 8-*trimethyl*-2-*oxo*-tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodec*-9-*yl acetate* (20 mg.), m. p. 182—183°, no high-intensity selective absorption in the ultra-violet above 220 mμ (Found : Br, 20·8. $C_{17}H_{25}O_3Br,CH_3{\cdot}OH$ requires Br, 20·6%).

iso*Caryophyllene Oxide*.—*iso*Caryophyllene was prepared *via* caryophyllene nitrosite by the method of Deussen and Lewinsohn (*Annalen*, 1907, **356**, 1). It had b. p. 92°/3 mm., and gave no nitrosite under the conditions used above for caryophyllene nitrosite and did not react with phenyl azide. Treatment in ethereal solution with perphthalic acid (110%) gave iso*caryophyllene oxide*, m. p. 80—81° [from light petroleum (b. p. 40—60°)], $[\alpha]_D$ −4° (*c*, 1·0) (Found : C, 81·95; H, 11·0. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%). The oxide gave a marked depression in m. p. on admixture with caryophyllene oxide, m. p. 61°, $[\alpha]_D$ −69° (*c*, 3·8).

*iso*Caryophyllene oxide (1·0 g.) in ethyl acetate (15 ml.) with palladised calcium carbonate (5%; 100 mg.) was hydrogenated until 1 mol. had been absorbed. The product was an oil which resisted all attempts at crystallisation (also after extensive chromatography). The oil (3·8 g.) in dioxan (5 ml.) and aqueous sulphuric acid (5 ml.; 10% w/v of sulphuric acid) was left at room temperature for 6 days. Working up and crystallisation from light petroleum (b. p. 40—60°) furnished a *glycol* (340 mg.), m. p. 165°, $[\alpha]_D$ −3° (*c*, 2·0) (Found : C, 75·2; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·75%). On titration with lead tetra-acetate the glycol took up 94% of the theoretical amount for one α-glycol system.

Similar hydrogenation of caryophyllene oxide afforded dihydrocaryophyllene oxide, m. p. 63—65° (Treibs, *Chem. Ber.*, 1947, **80**, 56). When this was subjected to the same acid-catalysed hydration no crystalline product could be obtained.

*Action of Nitrous Acid on Caryophyllene*.—Treatment of caryophyllene (50 g.) with nitrous acid according to Deussen and Lewinsohn (*loc. cit.*), removal of the precipitated nitrosite by filtration and washing of the residual light petroleum solution with aqueous sodium hydroxide (10%) gave a colourless oil. After distillation *in vacuo* there resulted almost pure *iso*caryophyllene (25 g.), b. p. 93°/3 mm., $\alpha_D$ −19°, characterised by conversion into the crystalline oxide (see above), identified by m. p., mixed m. p. and rotation {$[\alpha]_D$ −6° (*c*, 2·5)} by treatment with perphthalic acid.

*Hydration of* iso*Caryophyllene Oxide*.—The oxide (7 g.) was hydrated as described above for caryophyllene oxide. Crystallisation of the product from ether–light petroleum (b. p. 40—60° gave 4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-epi-*diol*, m. p. 174—175°, $[\alpha]_D$ +19° (*c*, 0·6) (Found : C, 75·15, H, 11·3. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%).

The glycol (200 mg.) in " AnalaR " acetic acid (2 ml.) was treated with a solution of chromium trioxide (105 mg.) in aqueous acetic acid (5 ml.; 90% v/v) for 5 hr. at room temperature. Filtration of the product in benzene through alumina and crystallisation from light petroleum (b. p. 40—60°) afforded 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]dodecane-2 : 9-dione (180 mg.) (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −106° (*c*, 0·8)}.

The glycol (200 mg.) in " AnalaR " acetic acid (2 ml.) was treated with chromium trioxide (48 mg.) in aqueous acetic acid (3 ml.; 90% v/v) for 3 hr. at room temperature. The product was chromatographed over alumina. Elution with benzene and crystallisation from light petroleum (b. p. 40—60°) furnished 4 : 4 : 8-*trimethyl*-2-*oxo*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecan*-9-epi-*ol* (90 mg.), m. p. 68—70°, $[\alpha]_D$ +31° (*c*, 0·6) (Found : C, 76·2; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

*Rates of Reaction with Perphthalic Acid*.—Caryophyllene, *iso*caryophyllene, and their respec-

tive dihydro-derivatives were titrated in an ice-bath with ethereal perphthalic acid. The reaction solutions were 0·0252M with respect to perphthalic acid and 0·023M with respect to the hydrocarbons. The data in the Table are illustrative.

*Reaction (%) with ethereal perphthalic acid.*

| Time (min.) | 76 | 243 | 360 | 48 × 60 |
|---|---|---|---|---|
| Caryophyllene (I) | 56 | 78 | 100 | — |
| *iso*Caryophyllene (X) | 10 | 20 | 43 | 80 |
| " Dihydrocaryophyllene " | 12 | 21 | 47 | 80 |
| " Dihydro*iso*caryophyllene " | 12 | 20 | 43 | 78 |

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited, for financial assistance. The clove-bud sesquiterpenes used for the extraction of caryophyllene were generously provided by Mr. Dewhurst of White, Tompkins, and Courage Ltd., Reigate, Surrey. One of us (A. A.) is indebted to the Stiftung für Stipendien auf dem Gebiete der Chemie for a Post-doctorate Fellowship. We thank Sir John Simonsen, F.R.S., for his interest in this work.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, June 4th, 1953.*]

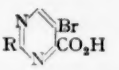
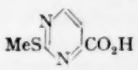
## 623. *Pyrimidines. Part VI.* 5-Bromopyrimidine.*

By J. F. W. McOMIE and I. M. WHITE.

5-Bromopyrimidine has been synthesised from 5-bromo-2-methylpyrimidine-4-carboxylic acid. Raney nickel desulphurisation of 5-bromo-2-methylthiopyrimidine-4-carboxylic acid yields pyrimidine-4-carboxylic acid and 2-methylthiopyrimidine-4-carboxylic acid; that of 5-bromo-2-methylthiopyrimidine yields pyrimidine.

5-BROMOPYRIMIDINE was required in connection with studies on the ultra-violet light absorption of pyrimidines (Boarland and McOmie, *J.*, 1952, 3716, 3722). Although many 5-bromopyrimidines are known the parent substance has not previously been prepared. An attempted preparation (Whittaker, *J.*, 1953, 1646) by catalytic dechlorination of 5-bromo-2 : 4-dichloropyrimidine gave only pyrimidine in unspecified yield.

The compound has now been synthesised from 5-bromo-2-methylpyrimidine-4-carboxylic acid (I; R = Me) which was obtained by condensation of acetamidine with mucobromic acid (Budešínský, *Coll. Czech. Chem. Comm.*, 1949, **14**, 223). The pyrimidine acid was smoothly decarboxylated by heat to 5-bromo-2-methylpyrimidine (II; R = Me) which with benzaldehyde in the presence of zinc chloride gave 5-bromo-2-styrylpyrimidine (II; R = Ph·CH:CH·). The same compound was obtained directly, but in poorer yield, from the pyrimidine acid (I; R = Me). The styryl compound was oxidised to the corresponding 5-bromopyrimidine-2-carboxylic acid (II; R = $CO_2H$) whence thermal decarboxylation gave 5-bromopyrimidine. Budešínský (*loc. cit.*) reported the oxidation of 5-chloro-2-methylpyrimidine-4-carboxylic acid by nitric acid to 5-chloropyrimidine-2 : 4-dicarboxylic acid. However, we were unable to oxidise the bromo-acid (I; R = Me) by nitric acid or potassium permanganate to the corresponding dicarboxylic acid (I; R = $CO_2H$), which might have been decarboxylated to the required 5-bromopyrimidine.

(I)  (II)  (III)

The synthesis of 5-bromopyrimidine was first attempted starting from 5-bromo-2-methylthiopyrimidine-4-carboxylic acid (I; R = MeS). The preparation of this compound from mucobromic acid and *S*-methylthiuronium sulphate was studied in detail. The highest yields (37%) were obtained by using 1-ethylpiperidine or triethylamine as condensing agent. Even so it was not possible to prepare more than *ca.* 1 gram of the methylthio-acid in each experiment without serious decrease in yield. Raney nickel

* Part V, *J.*, 1952, 4942.

desulphurisation of this acid (I; R = MeS) unexpectedly gave pyrimidine-4-carboxylic acid. Evidently the bromine atom is more labile than the methylthio-group since under milder conditions 2-methylthiopyrimidine-4-carboxylic acid (III) was produced. Simultaneous dehalogenation and desulphurisation also occurred when 5-bromo-2-methylthiopyrimidine (II; R = MeS) was treated with Raney nickel, thereby yielding pyrimidine, whereas similar treatment of 5-bromopyrimidine-2-carboxylic acid resulted in complete degradation or recovery of starting material. Catalytic dehalogenation of pyrimidines in presence of palladium is, of course, well known, but the only recorded use of Raney nickel (with or without added hydrogen) appears to be the dechlorination of 5-chloro-2-(*N*-*m*-aminobenzenesulphonyl-*N*-methylamino)pyrimidine by Raney nickel alloy in methanolic potassium hydroxide (English *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1039).

5-Bromo-2-methylpyrimidine was decomposed when heated with aqueous barium hydroxide. Under the same conditions 2-amino-5-bromo-4 : 6-dimethylpyrimidine was hydrolysed to the corresponding 5-hydroxypyrimidine (Bray, Lake, and Thorpe, *Biochem. J.*, 1951, **48**, 400).

The ultra-violet absorption spectra of 5-bromopyrimidine and of pyrimidine-4-carboxylic acid have already been published (Boarland and McOmie, *loc. cit.*). Data for the other compounds described in this paper are recorded in the Table.

| Substituents | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 | 4 | 5 | Solvent | $\lambda$ (m$\mu$) | $\log_{10} \varepsilon_{max.}$ | $\lambda$ (m$\mu$) | $\log_{10} \varepsilon_{max.}$ |
| Ph·CH:CH· | — | Br | EtOH | 228 | 4·11 | 235 | 4·04 |
| | | | | | | 308 | 4·57 |
| $CO_2H$ | — | Br | 0·1N-HCl | 242 | 4·33 | — | — |
| | | | 0·1N-NaOH | 231 | 3·97 | — | — |
| Me | $CO_2H$ | Br | 0·1N-NaOH | 222 | 3·98 | 271 | 3·62 |
| MeS | $CO_2H$ | — | 0·1N-NaOH | 253·5 | 4·19 | 303 | 3·29 |
| MeS | $CO_2H$ | Br | 0·1N-NaOH | 262·5 | 4·37 | 300 infl. | 3·41 |

## Experimental

*5-Bromo-2-styrylpyrimidine.*—5-Bromo-2-methylpyrimidine (Budešínský, *loc. cit.*) (5·6 g.), benzaldehyde (11·2 g.), and anhydrous zinc chloride (4·3 g.) were heated at 155—160° for 5—6 hr. After steam-distillation to remove benzaldehyde the product was collected in chloroform and purified by recrystallisation from light petroleum (b. p. 60—80°) (charcoal). *5-Bromo-2-styrylpyrimidine* (3·7 g., 44%) formed needles, m. p. 138—140° (Found: C, 55·3; H, 3·2; N, 10·8; Br, 31·2. $C_{12}H_9N_2Br$ requires C, 55·2; H, 3·5; N, 10·7; Br, 30·6%).

*5-Bromopyrimidine-2-carboxylic Acid.*—Finely powdered potassium permanganate (5·3 g.) and water (11 c.c.) were added separately during 1 hr. to a stirred solution of 5-bromo-2-styrylpyrimidine (3·0 g.) in pyridine (60 c.c.) and water (3 c.c.) at 14—15° (cooling). After being stirred for a further ½ hr. the solution was filtered through a thin bed of Filtercel, and the filter-cake washed with water. The filtrate was diluted with water, then concentrated to *ca.* 30 c.c. and acidified with concentrated hydrochloric acid. The solid was collected, washed with ether, and recrystallised from benzene (charcoal). The *bromo-acid* was obtained in 71% yield as the hemi-hydrate, m. p. 192—193° (Found: C, 28·5; H, 2·1; N, 13·0; Br, 37·6. $C_5H_3O_2N_2Br,\frac{1}{2}H_2O$ requires C, 28·3; H, 1·9; N, 13·2; Br, 37·7%).

*5-Bromopyrimidine.*—An evacuated sealed tube of 20-c.c. capacity containing the above bromo-acid (0·5 g.) was heated for 1½ hr. in an oil-bath at 250°. The product was sublimed at 80—90° (bath)/20 mm., giving *5-bromopyrimidine* (0·33 g., 85%) as prisms, m. p. 75—76° (Found: C, 29·8; H, 1·9; N, 17·5; Br, 49·8. $C_4H_3N_2Br$ requires C, 30·2; H, 1·9; N, 17·6; Br, 50·3%), slightly soluble in water and readily soluble in chloroform, ethanol, and ether It forms a crystalline complex with mercuric chloride.

*5-Bromo-2-methylthiopyrimidine-4-carboxylic Acid.*—*S*-Methylthiuronium sulphate (3·0 g.) was dissolved in a warm solution of mucobromic acid (2·8 g.) in water (43 c.c.), and then cooled to 18°. Triethylamine (3·3 g.) was added during 1 hr., with mechanical stirring. Next day a little concentrated hydrochloric acid was added to the solution, and the resulting tar removed by filtration. Further acidification gave a buff solid (1·0 g., 37%), m. p. 173—175°. Recrystallisation from water (charcoal) gave *5-bromo-2-methylthiopyrimidine-4-carboxylic acid* as pale yellow prisms, m. p. 176—177° (decomp.) (Found: C, 29·3; H, 2·0; N, 11·3; S, 12·8; Br, 31·5. $C_6H_5O_2N_2SBr$ requires C, 28·9; H, 2·0; N, 11·3; S, 12·9; Br, 32·1%).

*Desulphurisation of 5-Bromo-2-methylthiopyrimidine-4-carboxylic Acid.*—(*a*) The bromo-acid

(2 g.) in water (200 c.c.) was heated under reflux for 1¾ hr. with Raney nickel sludge (10 g.) (prepared by Brown's method, *J. Soc. Chem. Ind.*, 1950, **69**, 353), with mechanical stirring. The hot solution was filtered, and the solid washed with hot water (2 × 40 c.c.). The filtrate was concentrated to *ca.* 20 c.c. and set aside overnight. The yield of blue-green prisms of *nickel pyrimidine-4-carboxylate* was 0·65 g. (47·5%) (Found: C, 35·4; H, 2·9; N, 16·8; Ni, 16·7. $C_{10}H_6O_4N_4Ni,2H_2O$ requires C, 35·2; H, 3·0; N, 16·4; Ni, 17·2%). Pyrimidine-4-carboxylic acid (0·3 g.), obtained by the action of hydrogen sulphide on a solution of the nickel salt (0·65 g.), had m. p. 236—237° (decomp.; sealed capillary) (Found: C, 48·1; H, 3·5; N, 22·0. Calc. for $C_5H_4O_2N_2$: C, 48·4; H, 3·3; N, 22·6%). Gabriel and Colman (*Ber.*, 1899, **32**, 1535) give m. p. 240° (decomp.).

(*b*) The bromo-acid (1·0 g.) in water (100 c.c.) was desulphurised as above with Raney nickel sludge (3 g.) during 1¼ hr. The filtered solution yielded green prisms (0·31 g.) of a nickel salt, which was converted by hydrogen sulphide into the free acid (0·09 g.), m. p. 211—213° (decomp.). After three recrystallisations from benzene *2-methylthiopyrimidine-4-carboxylic acid* was obtained as needles (0·048 g.), m. p. 214—215° (decomp.) (Found: C, 42·6; H, 3·4; N, 16·6. $C_6H_4O_2N_2S$ requires C, 42·4; H, 3·6; N, 16·5%).

*5-Bromo-2-methylthiopyrimidine.*—5-Bromo-2-methylthiopyrimidine-4-carboxylic acid (2·0 g.) (unrecrystallised) was heated just above its m. p. until effervescence ceased. The 5-bromo-2-methylthiopyrimidine was sublimed and recrystallised from aqueous ethanol (charcoal), giving pale yellow leaflets (1·3 g.), m. p. 67°. A second crop (0·1 g.) m. p. 62—65°, was obtained from the mother-liquor, the total yield being 85%. A freshly sublimed sample was colourless and had m. p. 67—68° (Found: C, 29·6; H, 2·8; N, 13·5. Calc. for $C_5H_5N_2SBr$: C, 29·3; H, 2·5; N, 13·2%). Johnson and Joyce (*J. Amer. Chem. Soc.*, 1916, **38**, 1562) record m. p. 64—67° for the compound prepared by bromination of 2-methylthiopyrimidine.

*Desulphurisation of 5-Bromo-2-methylthiopyrimidine.*—5-Bromo-2-methylthiopyrimidine (1·0 g.) in ethanol (60 c.c.) and ammonia (1·0 c.c.; *d* 0·88) was heated under reflux with Raney nickel sludge (5·0 g.) for 2½ hr. To the filtered solution, after cooling, saturated aqueous mercuric chloride solution was added. The colourless crystals (0·65 g., 38%) had m. p. 230—237° depending on the rate of heating and were identified as pyrimidine mercurichloride by an *X*-ray powder photograph.

THE UNIVERSITY, BRISTOL. [*Received, June 22nd,* 1953.]

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## 624. *Anionotropic Systems. Part III.* The Synthesis and Rearrangement of 3-Hydroxy-3 : 5-dimethylhex-4-en-2-one.*

By E. A. BRAUDE and C. J. TIMMONS.

The first example of anionotropy in a three-carbon system terminated by a carbonyl group is described. As would be expected the anionotropic mobility of such a system is very low and the reaction succeeds only in a suitably designed structural environment.

Addition of *iso*butenyl-lithium to 3 : 3-dimethoxybutan-2-one furnished the ketal (XIII) which on mild acid hydrolysis gave 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (VIII). This βγ-ethylenic α-hydroxy-ketone undergoes anionotropic rearrangement under carefully controlled acid conditions, to the isomeric αβ-ethylenic γ-hydroxy-ketone (XIV), the structure of which is established by degradation. Prolonged acid treatment of (VIII) results in cyclisation to the dihydrofuran (XV), isolated as the ether (XVI), and dehydration to the dienone (XVII).

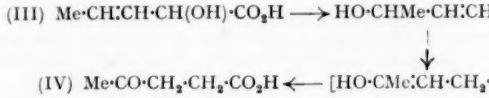
DURING the last ten years, many examples of anionotropic systems of the type

$$\text{(I)}\quad \text{C:C·CX·OH} \longrightarrow \text{C(OH)·C:C·X}\quad \text{(II)}$$

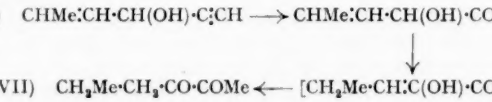
where X is one of a variety of unsaturated groups, including ethylenic, acetylenic, aromatic, and heteroaromatic functions, have been described (for a summary, see Braude, *Quart. Reviews*, 1950, **4**, 404). In all these rearrangements, the equilibrium is displaced almost completely to the right owing to the additional stabilisation associated with the conjugated

* Part II, *J.*, 1953, 2202.

systems C:CX. A carbonyl function should also have this effect, since its conjugating properties are well established, but the nearest example of such a reaction which appears in the literature involves X = $CO_2H$ and occurs in the conversion of 2-hydroxypent-3-enoic acid (III) into lævulic acid (IV) (Fittig and Schaak, *Annalen*, 1898, **299**, 42), where the anionotropic rearrangement is followed by a double prototropic change :



A possible route to a system of type (I) with X = COMe was investigated by Heilbron, Jones, Smith, and Weedon (*J.*, 1946, **54**; cf. Braude and Timmons, *J.*, 1953, **3144**) who attempted the hydration of the acetylenic alcohol (V) to the keto-alcohol (VI), but obtained instead the diketone (VII) formed by prototropic rearrangement under the acidic reaction conditions. These authors commented on the fact that the strongly electron-attracting properties of the carbonyl group would retard anionotropic rearrangement while favouring the alternative prototropic change, and their work indicated that anionotropic rearrangements of the type (I) ⟶ (II), where X is a ketone function, would be difficult, if not impossible, to realise.



Since the possible isomerisation of βγ-ethylenic α-hydroxy-ketones to αβ-ethylenic γ-hydroxy-ketones is of considerable practical as well as theoretical interest, we set out to produce a system with structural features more favourable to the occurrence of such a reaction. The simplest such is (VIII), in which complete alkylation in the α- and the γ-position will preclude prototropy, and at the same time increase anionotropic mobility (cf. Braude and Jones, *J.*, 1946, 122, 128). The synthesis of (VIII), and its acid-catalysed anionotropic rearrangement to (XIV), are described below. Kinetic studies, recorded in the following paper, show that the rate of isomerisation of (VIII) is slower by a factor of *ca.* $10^5$ than that of the corresponding phenyl analogue (Ph replacing COMe), in agreement with expectation.

The majority of standard methods for the synthesis of α-keto-alcohols are inapplicable to a system such as (VIII), but the monoaddition of *iso*butenyl-lithium (Braude and Timmons, *J.*, 1950, 2000, 2007; Braude and Coles, *J.*, 1952, 1425) to diacetyl appeared to afford a possible route. Only the diaddition product (IX) could be isolated, however, even when an excess of diacetyl was employed. Although the monoaddition of Grignard reagents to diacetyl is possible (cf. Wilson and Hyslop, *J.*, 1924, 1556; Kleinfeller and Eckert, *Ber.*, 1929, **62**, 1598; 1939, **72**, 249; Lapkin and Golovkova, *J. Gen. Chem., U.S.S.R.*, 1949, **19**, 701), the failure to effect monoaddition of the lithium-alkenyl is not altogether surprising, since lithium derivatives are known to be less selective than Grignard reagents in their action on polyfunctional compounds (cf. Carter, *Iowa State Coll. J. Sci.*, 1940, **15**, 63). An attempt to effect the monoaddition of *iso*butenylmagnesium bromide (Krestinsky, *Ber.*, 1922, **55**, 2773) to diacetyl was also unsuccessful; this Grignard reagent could only be formed in reasonable yield in the presence of methylmagnesium bromide, and the main products were 3-hydroxy-3-methylbutan-2-one $HO·CMe_2·COMe$ and the glycol (XII), although a small amount of (VIII) was also obtained. The structures of the ditertiary glycols (IX) and (XII) were established by fission with aqueous sodium periodate, which gave mesityl oxide in the first case, and acetone and mesityl oxide in the second. It is of interest that the reaction of the glycols (IX) and (XII) with sodium periodate is very slow and requires several days at room temperature; similar effects have been noted with other tertiary glycols (cf. Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923). With Brady's reagent the glycol (IX) slowly gave the 2 : 4-dinitrophenylhydrazone of a ketone evidently formed by pinacol–pinacone rearrangement. Since the ultra-violet

light absorption of the derivative ($\lambda_{max.}$ 3680 Å) shows that the functional group is not conjugated (cf. Braude and Jones, *J.*, 1945, 498), the ketone is formulated as (X) rather than (XI).

$$CMe_2{:}CH{\cdot}CMe(OH){\cdot}COMe \xleftarrow{CMe_2{:}CHLi} MeCO{\cdot}COMe \xrightarrow[MeMgBr]{CMe_2{:}CH{\cdot}MgBr} CMe_2{:}CH{\cdot}CMe(OH){\cdot}CMe_2{\cdot}OH$$
(VIII) (XII)

$$\downarrow CMe_2{:}CHLi$$

$$CMe_2{:}CH{\cdot}CMe(OH){\cdot}CMe(OH){\cdot}CH{:}CMe_2 \longrightarrow (CMe_2{:}CH)_2CMe{\cdot}COMe \qquad CMe_2{:}CH{\cdot}CMe_2{\cdot}CO{\cdot}CH{:}CMe_2$$
(IX) (X) (XI)

Attention was then directed to the addition of *iso*butenyl-lithium to a diacetyl derivative in which one of the carbonyl groups is temporarily protected. Reaction with diacetyl dimethyl monoketal (3 : 3-dimethoxybutan-2-one; Calder and Fleer, U.S.P. 2,401,336) afforded a moderate yield of the ketal (XIII). Mild acid hydrolysis (0·4M-sulphuric acid at room temperature) of the latter gave the desired keto-alcohol, 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (VIII). It was characterised by a 3 : 5-dinitrobenzoate and a 2 : 4-dinitrophenylhydrazone, the latter being prepared in pyridine instead of under the usual acid conditions.* The keto-alcohol and its 2 : 4-dinitrophenylhydrazone exhibited the ultra-violet light absorption characteristic of an isolated keto-group and its derivative.

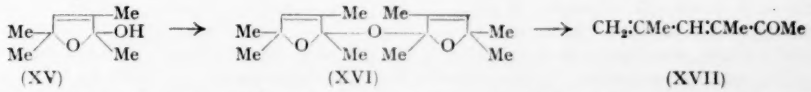
The anionotropic rearrangement of the $\beta\gamma$-ethylenic $\alpha$-hydroxy-ketone (VIII) to the isomeric $\alpha\beta$-ethylenic $\gamma$-hydroxy-ketone (XIV) was accomplished by treatment with 0·2M-sulphuric acid at 65° for 2 hr., optimum conditions having been found by trial experiments in which the reaction was followed spectrometrically (cf. following paper). 5-Hydroxy-3 : 5-dimethylhex-3-en-2-one (XIV) showed the expected ultra-violet light absorption ($\lambda_{max.}$ 2290 and 3160 Å) and was characterised by a 2 : 4-dinitrophenylhydrazone, prepared in dilute aqueous solution. Reaction of (XIV) with 2 : 4-dinitrophenylhydrazine sulphate in methanolic or ethanolic solution gave the derivatives of the corresponding methyl or ethyl ethers (XIV; OMe or OEt for OH), which could also be obtained directly from the unrearranged hydroxy-ketone (VIII) by treatment with the acidic reagent. The 2 : 4-dinitrophenylhydrazone of the ethyl ether of (XIV) is polymorphic; crystallisation from benzene–hexane gives an orange form which is slowly transformed into a red form of identical m. p.; recrystallisation of the red form again gives the metastable orange modification. The structure of the ketone (XIV) was confirmed by ozonolysis, which furnished diacetyl and $\alpha$-hydroxy*iso*butyraldehyde, isolated as the 2 : 4-dinitrophenylhydrazones.

$$Me{\cdot}CO{\cdot}CMe(OMe)_2 \xrightarrow{CMe_2{:}CHLi} CMe_2{:}CH{\cdot}CMe(OH){\cdot}CMe(OMe)_2 \quad (XIII)$$

$$\downarrow (a)\ 0{\cdot}4M\text{-}H_2SO_4,\ 20°$$

$$(XIV)\quad HO{\cdot}CMe_2{\cdot}CH{:}CMe{\cdot}COMe \xleftarrow[(b)]{0{\cdot}2M\text{-}H_2SO_4,\ 60°} CMe_2{:}CH{\cdot}CMe(OH{\cdot})COMe \quad (VIII)$$

$$\downarrow (c)$$

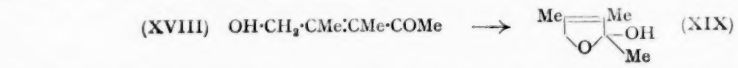



(XV) (XVI) (XVII)

When the acid treatment of (VIII) is prolonged beyond the optimum period, the yield of (XIV) decreases and after 26 hr. at 65° two different products are obtained. The main product is a much higher-boiling substance $C_{16}H_{26}O_3$ which contains no reactive hydrogen (Zerewitinoff), affords no 2 : 4-dinitrophenylhydrazone in the cold, and exhibits no high-intensity ultra-violet absorption. It is evidently the ether (XVI), produced by the cyclisation of the $\gamma$-hydroxy-ketone (XIV) to the dihydrofuran (XV), followed by self-etherification. The comparatively ready cyclisation of (XIV) is not unexpected; saturated

* No previous example of the preparation of a 2 : 4-dinitrophenylhydrazone under basic conditions, which may also be advantageous in other cases, appears to have been recorded.

γ-hydroxy-ketones are well-known to exist in equilibrium with the furanose form (cf. Helferich, *Ber.*, 1919, **52**, 1804; 1922, **55**, 702; 1924, **57**, 1911; Owen, *Ann. Reports*, 1945, **42**, 157) and an example more closely related to the present case has recently been recorded by Adams and Govindachari (*J. Amer. Chem. Soc.*, 1950, **72**, 158) who postulated the conversion of (XVIII) into (XIX) to explain the absence of functional reactivity. Other




examples of this type, involving the formation of phenyl-substituted 2 : 5-dihydrofurans have been described (Zalkind and Teterin, *J. pr. Chem.*, 1932, **133**, 195; Venus-Danilova *et al.*, *J. Gen. Chem., U.S.S.R.*, 1943, **13**, 93; 1947, **17**, 1549, 1849; 1949, **19**, 1755).

The second product obtained from the prolonged treatment of (VIII) with dilute sulphuric acid was a diethylenic ketone which was characterised by a 2 : 4-dinitrophenylhydrazone. The light absorption properties of the ketone ($\lambda_{max.}$ 2650 Å) indicate that it is the conjugated dienone (XVII), evidently formed by dehydration of (XIV) under the acid conditions. The dienone (XVII) was also obtained when the ether (XVI) was treated with 85% phosphoric acid, a method used by Woods and Temin (*J. Amer. Chem. Soc.*, 1950, **72**, 139) for the somewhat analogous conversion of bisdihydropyranyl ether into penta-2 : 4-dienal both ether fission and dehydration taking place.

The synthesis of (VIII) by the method outlined and its conversion into (XIV) clearly owe their success to the circumstance that the reactions (*a*) and (*c*), though also acid-catalysed, both have rates sufficiently different from that of the isomerisation (*b*) under appropriate conditions. The quantitative aspects and mechanisms of these changes are further discussed in the following paper.

## Experimental

M. p.s marked K were determined on a Kofler micro-melting point block and are corrected.

Light-absorption data were determined photographically on a Hilger-Spekker instrument. Active hydrogen values were determined by the modified Zerewitinoff method described by Braude and Stern (*J.*, 1946, 404). Oxygen analyses were carried out by Mr. F. H. Oliver by the method of Unterzaucher (*Ber.*, 1940, **73**, 391).

**2 : 4 : 5 : 7-*Tetramethylocta*-2 : 6-*diene*-4 : 5-*diol* (IX).**—Diacetyl (25 g.) in anhydrous ether (100 ml.) was slowly added with stirring and cooling in a cold-water bath to *iso*butenyl-lithium (Braude and Timmons, *J.*, 1950, 2000) (from Li, 10·5 g., and *iso*butenyl bromide, 102 g.) in anhydrous ether (1·5 l.) during ½ hr. The mixture was stirred for a further ½ hr. and an aqueous solution (400 ml.) of ammonium chloride (55 g.) was added. Isolation by means of ether and distillation gave two main fractions: one (10 g., 26%), b. p. *ca.* 30°/8 mm., on redistillation had b. p. 132—133°, m. p. 11°, $n_D^{19}$ 1·4780, being 2 : 5-dimethylhexa-2 : 4-diene (cf. Braude and Timmons, *loc. cit.*); the other was the crude *glycol* (15 g., 25%), b. p. 80—82°/0·2 mm., 115°/9 mm., $n_D^{17}$ 1·4907, which after several crystallisations from cold pentane, formed colourless needles, m. p. 57—61° (K) [Found: C, 70·6; H, 11·0%; *M* (Rast), 160; Active H, 1·76. $C_{12}H_{22}O_2.\frac{1}{2}H_2O$ requires C, 69·5; H, 11·1; O, 19·3%; *M*, 207]. The analytical data correspond to a *hemihydrate*, but were not appreciably changed after sublimation at $10^{-2}$ mm., which raised the m. p. to 65—71° (Found: C, 69·5; H, 11·1; O, 19·6%). The m. p. range also suggests the presence of a mixture of stereoisomers. Glacet (*Bull. Soc. chim.*, 1950, 16) gives b. p. 122—126°/11 mm., two forms, m. p.s 52·5° and 56°, but no analytical data. No significant amount of (VIII) was isolated either in this experiment or in experiments in which an excess of diacetyl was added to the *iso*butenyl-lithium solution or *vice versa* (so as to favour monocondensation).

*Periodate Oxidation of* **2 : 4 : 5 : 7-*Tetramethylocta*-2 : 6-*diene*-4 : 5-*diol*** (IX).—An aqueous solution (100 ml.) of the glycol (IX) (180 mg.) and sodium metaperiodate (300 mg.) was kept at room temperature for 1 week. The resulting solution was steam-distilled and the distillate was added to excess of 2 : 4-dinitrophenylhydrazine in aqueous ethanolic sulphuric acid. The precipitate was purified by chromatography on alumina from benzene–ethyl acetate and yielded 65 mg., which after recrystallisation from ethyl acetate had m. p. 202—203°, undepressed on admixture with the 2 : 4-dinitrophenylhydrazone of mesityl oxide. In one experiment the oxidation was allowed to proceed for only 1 hr. On working up as above, the 2 : 4-dinitrophenylhydrazone of 4-acetyl-2 : 4 : 6-trimethylhepta-2 : 5-diene (m. p. 130—132° undepressed

by the specimen obtained by direct acid treatment of the glycol) and not the derivative of mesityl oxide was isolated.

*Acid Treatment of* **2 : 4 : 5 : 7-***Tetramethylocta*-**2 : 6-***diene*-**4 : 5-***diol* (**IX**).—A solution (10 ml.) of the glycol (IX) (100 mg.) and 2 : 4-dinitrophenylhydrazine (100 mg.) in aqueous-ethanolic sulphuric acid was kept at room temperature for 2 hr. The **2 : 4-***dinitrophenylhydrazone* (45 mg.), after purification by chromatography on alumina from benzene–ethyl acetate, crystallised from aqueous methanol in orange crystals, m. p. 130—132°, and is formulated as the derivative of 4-acetyl-2 : 4 : 6-trimethylhepta-2 : 5-diene (X) (Found : C, 60·4; H, 6·8; N, 15·3. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·6%). Light absorption in $CHCl_3$ : Max. at 3680 Å; $\varepsilon = 28{,}000$.

*Reaction of* iso*Butenylmagnesium Bromide with Diacetyl*.—Methyl bromide (7 g.) was added with stirring to magnesium (48 g.) in anhydrous ether (1 l.) under nitrogen. When the reaction had commenced a mixture of *iso*butenyl bromide (135 g.) and methyl bromide (95 g.) in anhydrous ether (200 ml.) was added at such a rate as to give gentle refluxing under cooling in a cold-water bath. After the reaction was complete, the mixture was stirred for a further ½ hr. The flask was fitted with a specially designed hollow stirrer, lightly packed at the lower end with glass wool as previously described (Braude and Timmons, *loc. cit.*), so that the ethereal solution of the Grignard reagents could be forced through the stirrer by nitrogen into a separating funnel. The filtered Grignard solution was then added with stirring to diacetyl (170 g.) in anhydrous ether (300 ml.). The mixture was stirred overnight and decomposed by the addition of a saturated aqueous solution of ammonium chloride (400 g.) whilst cooled in a freezing mixture. Isolation by means of ether afforded a mixture which on fractionation yielded 3-hydroxy-3-methylbutan-2-one, impure 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (VIII) and **2 : 3 : 5-***trimethylhex*-**4-***ene*-**2 : 3-***diol* (**XII**). The butanone was obtained as a colourless oil (9 g.), b. p. 49—51°/17 mm., $n_D^{24}$ 1·4158 (Favorskii and Venscheidt, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1361; *J. pr. Chem.*, 1913, **88**, 662, give b. p. 50°/18 mm., *n* 1·415) (Found : C, 58·3; H, 9·7%; active hydrogen, 0·92 atom. Calc. for $C_5H_{10}O_2$ : C, 58·7; H, 9·9%). Light absorption in EtOH : Max. at 2810 and 2910 Å; inflection at 2560 Å; $\varepsilon = 26$, 26, and 64 respectively. The semicarbazone had m. p. 162—165° (Favorskii and Venscheidt, *loc. cit.*, give m. p. 164—165°). Light absorption in ethanol : Max. 2235 Å; $\varepsilon = 14{,}300$. The yellow **2 : 4-***dinitrophenylhydrazone*, crystallised from aqueous methanol, had m. p. 71—72° (Found : N, 20·2. $C_{11}H_{14}O_5N_4$ requires N, 19·9%). Light absorption in $CHCl_3$ : Main max. at 3550 Å; $\varepsilon = 22{,}900$. The crude 3-hydroxy 3 : 5-dimethylhex-4-en-2-one (10 g.) had b. p. 58—66°/17 mm., $n_D^{24}$ 1·4448—1·4467, and was identified by the formation of the 2 : 4-dinitrophenylhydrazone of the methyl ether of (XIV) on reaction with an aqueous-methanolic sulphuric acid solution of 2 : 4-dinitrophenylhydrazine (cf. below). The glycol (XII) distilled over as a viscous oil (12 g.), b. p. 102—105°/20 mm., 113—115°/25 mm., which slowly crystallised in a refrigerator. Recrystallisation from pentane afforded colourless needles, m. p. 33—37° [Found : C, 68·0, 67·5; H, 11·1, 11·3%; *M* (Rast), 136; active hydrogen : 2·08 atoms. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%; *M*, 158].

*Periodate Oxidation of* **2 : 3 : 5-***Trimethylhex*-**4-***ene*-**2 : 3-***diol*.—A solution of the glycol (XI) (200 mg.) and sodium metaperiodate (500 mg.) in water (15 ml.) was kept at room temperature for 6 days. After steam-distillation, the ketones were converted into their 2 : 4-dinitrophenylhydrazones, separated by chromatography from benzene on alumina and identified by the m. p.s of the derivatives [acetone, m. p. 121—124° (7 mg.), and mesityl oxide, m. p. 200—202° (40 mg.)], both undepressed on admixture with authentic samples. If the reaction mixture was kept for only 17 hr. before steam-distillation, no appreciable oxidation occurred.

**3 : 3-***Dimethoxybutan*-**2-***one*.—Freshly distilled diacetyl (300 g.) was refluxed for ½ hr. with absolute methanol (1500 ml.) containing ammonium chloride (6 g.) and set aside overnight (cf. Calder and Fleer, U.S.P., 2,401,336). The mixture was made alkaline with dilute sodium carbonate solution and fractionated through a 14″ Fenske column. After distillation of the methanol and ketal–water mixture, water (100 ml.) was added to the residue and fractionation afforded a further amount of ketal–water mixture. The fraction of b. p. 88—98° separated into two layers. The top layer of ketal (70 g.) was separated and the bottom layer, together with all the other fractions, was extracted with light petroleum (b. p. 40—60°) continuously for a week. The light petroleum layer was separated and evaporated through a column. The combined crude ketal fractions were dried ($Na_2SO_4$) and fractionated, to give the ketal (200 g., 57%) as a colourless liquid, b. p. 145—146°, $n_D^{18}$ 1·4084 (Calder and Fleer, *loc. cit.*, give b. p. 145° and do not state the yield). Light absorption in ethanol : Max. at 2960 Å; $\varepsilon = 26{\cdot}4$.

**3 : 3-***Diethoxybutan*-**2-***one*.—A solution of diacetyl (200 ml.) and concentrated sulphuric acid

(2 ml.) in absolute ethanol (1 l.) was kept overnight and afterwards poured into aqueous sodium hydroxide (50 g. in 2 l.). The resulting solution was carefully fractionated. Since none of the fractions separated into two layers (cf. Calder and Fleer, *loc. cit.*), the total distillate was extracted with ether. The ethereal solution was dried ($Na_2SO_4$) and the ether removed by slow distillation through a 14" Fenske column. Fractionation of the residue afforded **3** : 3-diethoxybutan-2-one (11 g., 5%), which on redistillation had m. p. 164°, $n_D^{18}$ 1·4109. Light absorption: In EtOH, max. at 2910 Å ($\varepsilon = 42$); in hexane, max. at 2900 Å ($\varepsilon$ 40). Calder and Fleer (*loc. cit.*) obtained 200 ml., of b. p. 163—165°. Harris (*J.*, 1950, 2247) records $n_D^{25}$ 1·4033 and light absorption (solvent not stated): Max. at 2940 Å; $\varepsilon = 34$.

**2** : 2-*Dimethoxy*-3 : 5-*dimethylhex*-4-*en*-3-*ol* (XIII).—**3** : 3-Dimethoxybutan-2-one (165 g.) in anhydrous ether (200 ml.) was added to *iso*butenyl-lithium (from Li, 21·1 g., and *iso*butenyl bromide, 220 g.; Braude and Timmons, *loc. cit.*) in anhydrous ether (3 l.). After being stirred overnight, the mixture was cooled to 0° and a saturated aqueous solution of ammonium chloride (83 g.) was added. Isolation with ether and fractionation gave a product (61 g., 26%), b. p. 112°/35 mm., which on refractionation afforded **2** : 2-*dimethoxy*-3 : 5-*dimethylhex*-4-*en*-3-*ol* as a colourless oil, b. p. 100°/16 mm., $n_D^{24}$ 1·4538 (Found: C, 64·5; H, 10·7; Active H, 0·93 atom. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·7%).

In one experiment in which the *iso*butenyl-lithium solution was filtered (cf. Braude and Timmons, *loc. cit.*) and added to the ethereal solution of the ketal no appreciable yield of (XIII) could be isolated.

3-*Hydroxy* **3** : 5-*dimethylhex*-4-*en*-2-*one* (VIII).—**2** : 2-Dimethoxy-3 : 5-dimethylhex-4-en-3-ol (73 g.) was shaken overnight with 2% (v/v) aqueous sulphuric acid (500 ml.). Isolation by means of ether and fractionation gave 3-*hydroxy*-3 : 5-*dimethylhex*-4-*en*-2-*one* as a colourless liquid (46 g., 83%), b. p. 80·5—80·7°/16 mm., $n_D^{25}$ 1·4508 (Found: C, 67·3; H, 10·1. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). Light absorption in hexane: Max. 2800 Å; $\varepsilon = 227$. Light absorption in 40% aqueous ethanol: Max. at 2810 Å; $\varepsilon = 227$. The *semicarbazone*, crystallised from water, had m. p. 154—157° (Found: N, 21·3. $C_9H_{17}O_2N_3$ requires N, 21·1%). Light absorption in EtOH: Max. at 2260 Å; $\varepsilon = 17{,}200$. These data correspond to the derivative of a saturated ketone; thus acetone semicarbazone shows $\lambda_{max.}$ 2240 Å ($\varepsilon$ 12,000), *cyclo*hexanone semicarbazone $\lambda_{max.}$ 2280 Å ($\varepsilon$ 13,000), and 3-hydroxy-3-methylbutan-2-one semicarbazone $\lambda_{max.}$ 2235 Å ($\varepsilon$ 14,300). The **2** : 4-*dinitrophenylhydrazone* was prepared by refluxing a solution of the hydroxy-ketone (1 g.) and 2 : 4-dinitrophenylhydrazine (1·5 g.) in anhydrous pyridine (5 ml.) for about 3 min. and then allowing the reaction mixture to cool to room temperature. Benzene (20 ml.) was added and the resulting solution was chromatographed on alumina. Elution with benzene–ethyl acetate gave the derivative as an oil, which after crystallisation from benzene–hexane as orange needles had m. p. 107—109° (K) (1·1 g.) (Found: C, 52·5; H, 5·7; N, 17·3. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%). Light absorption in $CHCl_3$: Main max. 3580 Å; $\varepsilon = 22{,}700$. The **3** : 5-*dinitrobenzoate* crystallised from hexane as colourless prisms, m. p. 96—99° (K) (Found: C, 53·7; H, 5·3; N, 8·4. $C_{15}H_{16}O_7N_2$ requires C, 53·6; H, 4·8; N, 8·3%). Light absorption in EtOH: Max. at 2270 Å; inflection at 2330 Å; $\varepsilon = 23{,}500$ and 20,900 respectively.

5-*Hydroxy*-3 : 5-*dimethylhex*-3-*en*-2-*one* (XIV).—A mixture of 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (20 g.) and 1% (v/v) aqueous sulphuric acid (400 ml.) was maintained at 65° for 2½ hr. and then cooled to room temperature and was extracted with ether. The extract was washed with dilute aqueous sodium carbonate and dried ($Na_2SO_4$–$K_2CO_3$). After distillation of the ether, the residue on fractionation afforded unchanged 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (7 g.) and 5-*hydroxy*-3 : 5-*dimethylhex*-3-*en*-2-*one* (8·5 g., 42%) as a colourless oil, which on refractionation had b. p. 69—70·5°/0·3 mm., $n_D^{19}$ 1·4759 (Found: C, 67·4; H, 10·1. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). Light absorption in EtOH: Max. at 2290 Å ($\varepsilon$ 11,000); inflection at 3090 Å ($\varepsilon$ 45). Light absorption in dioxan: Max. at 2290 Å ($\varepsilon$ 11,400); inflection at 3160 Å ($\varepsilon = 45$). Treatment with **2** : 4-dinitrophenylhydrazine in aqueous-ethanolic sulphuric acid gave a mixture which was separated by chromatography from benzene on alumina and afforded the **2** : 4-*dinitrophenylhydrazones* of (XIV) and of the ethyl ether of (XIV). The former derivative crystallised from benzene–hexane in red plates, m. p. 155—156° (K) (Found: C, 52·1; H, 5·6; N, 17·4. $C_{14}H_{18}O_5N_4$ requires C, 52·1; H, 5·6; N, 17·4%). Light absorption in $CHCl_3$: Max. at 2560, 2800, 3780 Å; inflection at 2920 Å; $\varepsilon$ = 16,500, 12,300, 28,000, and 9000 respectively. The latter derivative crystallised from benzene–hexane in orange needles, m. p. 152—153° (K) (Found: C, 54·8; H, 6·6; N, 16·0. $C_{16}H_{22}O_5N_4$ requires C, 54·8; H, 6·3; N, 16·0%). Light absorption in $CHCl_3$: Max. at 2560, 2900, and 3780 Å; inflection at 2800 Å; $\varepsilon$ = 20,000, 12,300, 30,600, and 14,700 respectively. This derivative, when allowed to stand

with solvent, after crystallisation changed slowly to light red needles, m. p. 152—153°, undepressed by the orange form and showing light absorption properties in chloroform and analytical data similar to those of the orange form. On recrystallisation the red reverted to the orange form. The 2 : 4-dinitrophenylhydrazones of (XIV) and of its ethyl ether were also obtained by treating (VIII) with 2 : 4-dinitrophenylhydrazine in aqueous-ethanolic sulphuric acid. When aqueous-methanolic sulphuric acid was used the 2 : 4-*dinitrophenylhydrazone* of the methyl ether of (XIV) was prepared. It crystallised from benzene–hexane in orange prisms, m. p. 168—170° (K) (Found: C, 53·9; H, 6·1; N, 16·7. $C_{15}H_{20}O_5N_4$ requires C, 54·0; H, 6·0; N, 16·7%). Light absorption in $CHCl_3$: Main max. at 3780 Å; $\varepsilon = 27{,}500$.

*Ozonolysis of* 5-*Hydroxy*-3 : 5-*dimethylhex*-3-*en*-2-*one* (XIV).—Ozonolysis of (XIV) (0·9 g.) by the method of Church, Whitmore, and McGrew (*J. Amer. Chem. Soc.*, 1932, **54**, 3710; 1934, **56**, 176) and conversion of the carbonyl compounds formed into their 2 : 4-dinitrophenylhydrazones afforded the derivative of α-hydroxy*iso*butyraldehyde, which after chromatography from chloroform on alumina, crystallised from benzene–hexane in yellow needles (75 mg.), m. p. 188—191° (K) undepressed on admixture with an authentic specimen prepared as described below.

There was also obtained the *bis*-2 : 4-*dinitrophenylhydrazone* of diacetyl which crystallised from ethanol–nitrobenzene in orange needles (90 mg.), m. p. 346—349° (K) (Matthiessen and Hagedorn, *Mikrochem. Mikrochim. Acta*, 1941, **29**, 60, give m. p. 335—338° but report no analytical data), undepressed by an authentic sample (Found: C, 43·3; H, 3·5; N, 24·9. $C_{16}H_{14}O_8N_8$ requires C, 43·1; H, 3·2; N, 25·1%). Light absorption in $CHCl_3$: Max. at 3950 and 4360 Å; $\varepsilon = 40{,}000$ and 37,000 respectively.

α-*Hydroxy*isobutyraldehyde.—Addition of bromine to a solution of freshly distilled *iso*butyraldehyde (51 g.), b. p. 63—64° ($\lambda_{max.}$ in hexane 2900 Å, $\varepsilon = 15{\cdot}5$), in carbon disulphide (700 ml.) was continued until the bromine colour persisted. The carbon disulphide was removed by distillation and the residue was further distilled, to give almost pure α-bromo*iso*butyraldehyde (cf. Franke, *Monatsh.*, 1900, **21**, 205, 210). The middle fraction had b. p. 86·5—92°/310 mm., $n_D^{20}$ 1·4738. Light absorption in hexane: Max. at 2980 Å; $\varepsilon = 35{\cdot}0$. A mixture of α-bromo-*iso*butyraldehyde (29 g.) and water (400 ml.) was refluxed until homogeneous. After cooling and neutralisation with 2N-sodium hydroxide the product was extracted with ether. The extract was dried ($Na_2SO_4$) and the ether removed. Fractionation of the residue gave α-hydroxy*iso*-butyraldehyde as a colourless liquid, b. p. 88—95°/140 mm., $n_D^{19}$ 1·4424 (cf. Franke, *ibid.*, pp. 213 and 1127). Light absorption in hexane: Max. at 2710 and 2810 Å; $\varepsilon = 22$. The 2 : 4-*dinitrophenylhydrazone* was chromatographed on alumina from benzene–chloroform and crystallised from benzene–chloroform or benzene–hexane in yellow needles, which sublimed and had m. p. 188—191° (K) (Found: C, 45·1; H, 4·7; N, 21·0. $C_{10}H_{12}O_5N_4$ requires C, 45·1; H, 4·5; N, 19·9%). Light absorption in $CHCl_3$: Main max. at 3530 Å; $\varepsilon = 24{,}000$. Campbell (*J. Amer. Chem. Soc.*, 1937, **59**, 1980) reports orange-red needles, m. p. 142°, which did not give satisfactory analyses.

*Di*-(2 : 3 : 5 : 5-*tetramethyl*-2 : 5-*dihydro*-2-*furyl*) *Ether* (XVI) *and* 3 : 5-*Dimethylhexa*-3 : 5-*dien*-2-*one* (XVII).—3-Hydroxy-3 : 5-dimethylhex-4-en-2-one (6 g.) and 1% (v/v) aqueous sulphuric acid (200 ml.) were kept at 65° for 26 hr. Isolation of the products as in the preparation of 5-hydroxy-3 : 5-dimethylhex-3-en-2-one afforded two fractions. The first was impure 3 : 5-dimethylhexa-3 : 5-dien-2-one (XVII), a colourless oil (0·5 g.), b. p. 77°/10 mm., $n_D^{17}$ 1·4830. Light absorption in EtOH: Max. 2510, 2580, and 2650 Å; $\varepsilon = 5200$, 5200 and 6800 respectively. The 2 : 4-*dinitrophenylhydrazone*, after chromatography on alumina with benzene–ethyl acetate, crystallised from benzene–hexane in red prisms, m. p. 176° (K) (Found: C, 55·3; H, 5·6; N, 18·2. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3; N, 18·4%). Light absorption in $CHCl_3$: Max. at 2580, 2670, 2810, 2920, and 3870 Å; $\varepsilon = 17{,}000$, 17,000, 14,300, 14,300, and 33,500 respectively. The main fraction (2·2 g.) was *di*-(2 : 3 : 5 : 5-*tetramethyl*-2 : 5-*dihydro*-2-*furyl*) *ether*, a colourless viscous oil, b. p. 107—110°/0·6 mm., $n_D^{17}$ 1·4710 [Found: C, 72·1; H, 9·8%; *M* (Rast), 240. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8%; *M*, 266]. Light absorption in hexane: Max. at 2280 Å; inflection at 2640 Å; $\varepsilon = 1480$ and 320 respectively. Some crystals were slowly deposited, which crystallised from pentane–ether in colourless needles, m. p. 178—181° (K) (Found: C, 71·5; H, 10·0%; *M*, 243). The ether gave no effervescence with a solution of methyl-magnesium iodide in ether and did not form a 2 : 4-dinitrophenylhydrazone in the cold. Several attempts to isolate the 2 : 3 : 5 : 5-tetramethyl-2 : 5-dihydrofuran-2-ol itself, by carrying out the cyclisation with a more dilute solution of the rearranged hydroxy-ketone (XIV) (*e.g.*, 1%), were unsuccessful, only the dienone (XVII) and the ether (XVI) being obtained (cf. Braude, Fawcett, and Newman, *J.*, 1950, 793).

*Fission and Dehydration of Di-(2 : 3 : 5 : 5-tetramethyl-2 : 5-dihydro-2-furyl) Ether.*—The ether (XVI) (1·4 g.) was added to an aqueous solution (14 ml.) of 85% phosphoric acid (4 ml.) and the mixture was steam-distilled (cf. Woods and Temin, *J. Amer. Chem. Soc.*, 1950, **72**, 139). From the steam-distillate 3 : 5-dimethylhexa-3 : 5-dien-2-one was isolated as the 2 : 4-dinitrophenylhydrazone, which after chromatographic purification and crystallisation (135 mg.) had m. p. 172—173° (K) undepressed by the specimen obtained as a by-product in the preparation of the ether (XVI).

Most of the work described in this and the following two papers was carried out during 1947—1949 while one of us (C. J. T.) was in receipt of a D.S.I.R. maintenance grant, which is gratefully acknowledged.

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## 625. *Anionotropic Systems. Part IV.* The Kinetics of the Rearrangement of 3-Hydroxy-3 : 5-dimethylhex-4-en-2-one. The Effect of an Acetyl Group on Anionotropic Mobility.*

By E. A. BRAUDE and C. J. TIMMONS.

A kinetic study has been made of the acid-catalysed rearrangement of the α-hydroxy-βγ-ethylenic ketone (I) to the γ-hydroxy-αβ-ethylenic ketone (II) and of the cyclisation of the latter to the dihydrohydroxyfuran (III).

The anionotropic change C:C·C(OH)·C:O ⟶ C(OH)·C:C·C:O exhibits mechanistic features analogous to those found with other allyl alcohols, except for effects arising from the strong solvation of the acetyl group in aqueous solvents, but the mobility of the system is the lowest yet encountered and provides a measure of the strong electron-attracting properties of the acetyl group.

The cyclisation reaction C(OH)·C:C·C:O ⟶ C·C:C·C(OH) has a rate similar to that of the rearrangement in 40% aqueous dioxan, but shows quite a different dependence on solvent composition, being accelerated by increasing dioxan content. A mechanism for the cyclisation reaction is discussed which accounts for the solvent dependence in terms of the effects of the solvation of the acetyl group on the equilibrium between the *cis*- and the *trans*-form of the oxonium ion (II*a*).

IN the preceding Part,* the anionotropic rearrangement of 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (I) to 5-hydroxy-3 : 5-dimethylhex-3-en-2-one (II) and the subsequent cyclisation of the latter to the dihydrohydroxyfuran (III) were described. In the present communication, a quantitative investigation of these reactions is reported.

$$CMe_2{:}CH{\cdot}CMe(OH){\cdot}COMe \longrightarrow HO{\cdot}CMe_2{\cdot}CH{:}CMe{\cdot}COMe \longrightarrow Me_2\langle\overset{Me}{O}\rangle\overset{Me}{\underset{OH}{}}$$

(I) (II) (III)

The rate measurements were carried out spectrometrically, by following the appearance and subsequent disappearance of the intense absorption band at 2290 Å associated with the conjugated (C:C·C:O) system present in the keto-alcohol (II). The progress of the two consecutive reactions is evident from a plot of the extinction coefficient at 2290 Å against time (Fig. 1). Under favourable conditions, with 40% aqueous dioxan as reaction medium, the absorption intensity rises to a maximum value corresponding to about 50% of (II) and the slope of the rising, left-hand part of the curve is rather steeper than that of the falling right-hand part, showing that the rate of rearrangement is slightly faster than the cyclisation under these conditions. In order to obtain results comparable with previous data on allied reactions, however, some of the kinetic measurements were made

* Part III, preceding paper.

with 60 and 80% aqueous dioxan solvents, in which cyclisation is about as fast as, or even faster than, rearrangement, so that the concentration of the rearranged keto-alcohol (II) rarely reached more than about 30% of the total. The rearrangement was therefore followed in detail over the first third of the reaction, and first-order rate constants ($k_R$) were calculated by taking the actual value of $\varepsilon_{max.}$ of the conjugated keto-alcohol (II) as the end-point, and were extrapolated to zero time (see Experimental). Approximate rate constants ($k_C$) for the cyclisation could be derived from the decrease of $k_R$ as the reaction progresses, or from the falling branch of the curves of $\varepsilon$ against time, but were more conveniently determined separately, a pure sample of the rearranged keto-alcohol (II) being used.

*The Anionotropic Rearrangement.*—The kinetic features of the rearrangement (I) ⟶ (II) are essentially analogous to those observed in the anionotropy of other substituted allyl alcohols (cf. Braude, *J.*, **1948**, **794**; *Ann. Reports*, **1949**, **46**, 114). In aqueous dioxan–hydrochloric acid, the rate constants are approximately proportional to the acid concentration at low acidities and decrease with increasing dioxan content of the medium, being lower by factors of 2—3 in 60%, compared with those in 40%, aqueous dioxan. The

FIG. 1. *Rearrangement of* (I) *in* 40% *aqueous dioxan–*0·1M*-hydrochloric acid at* 80°.

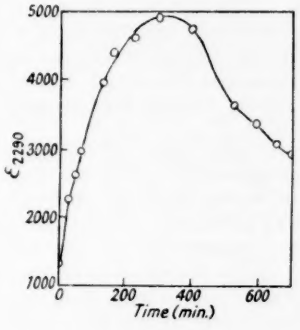
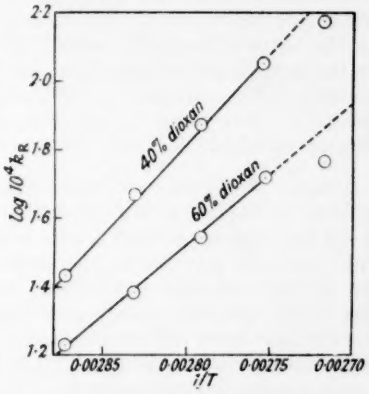



FIG. 2. *Arrhenius plots for the rearrangement of* (I) *in* 40% *and* 60% *aqueous dioxan–*0·1M*-hydrochloric acid.*




plots of log $k_R$ for 40 and 60% dioxan–0·1M-hydrochloric acid against $1/T$ gave straight lines in the 75—90° range, and the Arrhenius energies of activation are 25 and 19 kcal./mole respectively (Table 1). Measurements were also made at 95°, but, although reproducible

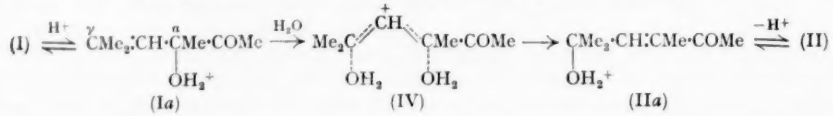
TABLE 1. *First-order rate constants* ($k_R$ *in min.*$^{-1}$) *for the rearrangement* (I) ⟶ (II) *in aqueous dioxan–hydrochloric acid.* $c_A$ = *acid concn.* (*mole/l.*).

| | (*a*) *In* 40% *aqueous dioxan* † | | | | (*b*) *In* 60% *aqueous dioxan* † | | | |
|---|---|---|---|---|---|---|---|---|
| *t* | $c_A$ | $c_{ROH}$ | $10^4 k_R$ | $k_R/c_A$ | $c_A$ | $c_{ROH}$ | $10^4 k_R$ | $k_R/c_A$ |
| 75° | 0·1 | 0·13 | 27·5 | 0·0275 | 0·1 | 0·13 | 16·9 | 0·0169 |
| 80 | 0·1 | 0·13 | 46·5 | 0·0465 | 0·1 | 0·13 | 24·3 | 0·0243 |
| 85 | 0·1 | 0·13 | 74·5 | 0·0745 | 0·1 | 0·13 | 34·7 | 0·0347 |
| | | | | | 0·1 | 1·3 | 33·5 | 0·0335 |
| | | | | | 0·2 | 0·13 | 71·5 | 0·0357 |
| 90 | 0·1 | 0·13 | 113 | 0·113 | 0·1 | 0·13 | 52 | 0·052 |
| | | | | | 0·2 | 0·13 | 110 | 0·055 |
| 95 | 0·1 | 0·13 | 150 * | 0·150 | 0·1 | 0·13 | 58 * | 0·058 |
| | $E_{Arr.}$ = 24·6 kcal./mole. | | | | $E_{Arr.}$ = 19·3 kcal./mole. | | | |

* Omitted in the evaluation of $E_{Arr.}$ † For details of solvent composition, see Experimental.

values were obtained, they fall appreciably below the Arrhenius plots (Fig. 2). A similar deviation above 90° was observed in the rearrangements of 1-ethynyl-3-methylallyl alcohol (hex-2-en-5-yn-3-ol) and its acetate in the same media (Braude, *loc. cit.*, 1948). This effect is most probably due to a partial breakdown of the hydrogen-bonded " structure " of

the solvent on approaching the boiling point, and a consequent decrease in the acidity function (cf. Braude and Stern, *Nature*, 1948, **161**, 169; *J.*, 1948, 1976).



There is no reason to doubt that the anionotropic rearrangement of (I) proceeds by the same mechanism as that of other allyl alcohols under similar conditions, namely, bimolecular attack by a solvent water molecule at the γ-carbon atom of the oxonium ion (I*a*) (Braude, *loc. cit.*). The expression (IV) represents the *transition state* in which the migration of the positive charge is half-completed and which should be clearly differentiated from the solvated form of an allyl cation *intermediate* (cf. Dewar, *Ann. Reports*, 1951, **48**, 123). One noteworthy point of difference, however, between the rearrangement of (I) and of other allyl alcohols previously studied is that, in the present case, the energy of activation is lower in 60% than in 40% aqueous dioxan (cf. Braude and Stern, *J.*, 1947, 1096). This may be explained in terms of the aqueous solvation of the carbonyl group which will be much more marked than that of other less highly polar conjugating groups such as aryl, alkenyl, etc. The acetyl group has a strongly retarding influence on the rearrangement (see below) which will be much reduced by solvation, as can be seen by considering the extreme hydrated form ·$CMe(OH)_2$. This hydrated form is not readily detected in the keto-alcohols themselves, the ultra-violet-light absorption of which shows little dependence on the water content of the medium, but will be greatly enhanced in the oxonium ions (I*a*; II*a*) owing to the effect of the positive charge (cf. the formation of stable hydrates by aldehydes and ketones, *e.g.*, chloral, containing strongly electron-attracting groups). Now, the equilibrium ·CMe:O $\overset{H_2O}{\rightleftharpoons}$ ·$CMe(OH)_2$ in the oxonium ion (I*a*) will be displaced to the left with increase in temperature, and it will be so displaced more rapidly in the less aqueous solvent which is less highly associated (cf. Braude and Stern, *loc. cit.*, 1948) and will give rise to the larger heat of solvation. Thus, the temperature dependence of the solvation equilibrium will be superimposed on the other factors contributing to the observed energy of activation. Since the unsolvated species will be the less reactive, the rates will increase *less* rapidly with temperature than they would in the absence of solvation, *i.e.*, the observed energies of activation will be smaller and more markedly so in the less aqueous solvent.

The main interest of the rate data for the rearrangement attaches to a comparison of the mobility of the system with that of analogues containing different conjugating substituents. Table 2 shows that the rate of rearrangement of the keto-alcohol (I) is

TABLE 2.

| | Me·CO·CMe(OH)·CH:$CMe_2$ | Ph·CMe(OH)·CH:$CMe_2$ | CHMe:CH·CMe(OH)·CH:$CMe_2$ |
|---|---|---|---|
| $k'_R$ [1] ..... | 0·00027 [2] | 7·4 [3] | 37·00 [3] |
| | Me·CO·$CO_2$H | Ph·$CO_2$H | CHMe:CH·$CO_2$H |
| $10^5K$ [4] ..... | 320 | 6·3 | 2·04 |

[1] Specific rate constants ($k_R/c_A$; min.$^{-1}$) for 60% aqueous dioxan–hydrochloric acid at 30°. [2] Extrapolated from measurements at higher temperatures. [3] Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1952, 1425; and unpublished work. [4] Dissociation constants in water at 25°.

slower by several powers of ten than that of analogues containing aryl or alkenyl substituents in place of the acetyl group. It is well established that anionotropy is facilitated by electron-donating and retarded by electron-attracting substituents, and the exceptionally low mobility of (I) provides a quantitative measure of the strong electron-attracting properties of the carbonyl group. Qualitatively, these are well established, *e.g.*, from the predominant *meta*-direction of the electrophilic substitution of aryl ketones, but the only other quantitative evidence appears to come from the dissociation of α-keto-acids (Böeseken, Hansen, and Bertram, *Rec. Trav. chim.*, 1916, **35**, 313) and from nucleophilic substitution reactions (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 488; Bunnett

and Zahler, *Chem. Reviews*, 1951, **49**, 308) in which the acetyl group exerts a facilitating influence. Thus, pyruvic acid is a much stronger acid than benzoic or crotonic (Table 2).

A plot of log $(k_R/c_A)$ for the anionotropic rearrangements of a more extended series of substituted allyl alcohols CMeR':CH·CRX·OH against the logarithms of the dissociation constants of the acids X·$CO_2$H reveals (Fig. 3) an approximately inverse relationship of the type first established by Hammett (*Chem. Reviews*, 1935, **17**, 125; cf. Burkhardt, Ford, and Singleton, *J.*, 1936, 17) for substituted phenyl derivatives. (The data are taken from Braude and Stern, *J.*, 1947, 1096; Braude and Fawcett, *J.*, 1950, 800; 1952, 4158; and Table 2.) Since the degree of alkyl substitution is not the same in each alcohol, the specific rate constants have been "normalised" by adding or subtracting an appropriate increment when R or R' = Me. It is notable that, in the present instance, the correlation extends over a rate range of $10^8$ and includes not only X = phenyl, *m*- and *p*-substituted phenyl, and 2-naphthyl, but also X = vinyl, propenyl, and acetyl. On the other hand, the correlation does not include X = *o*-tolyl, 1-naphthyl, 9-anthryl and 9-phenanthryl, 2-thienyl and 2-furyl, and ethynyl and hexynyl; in each of these cases the carboxylic acid is weaker than would be predicted from the anionotropic mobility of the allyl alcohol if

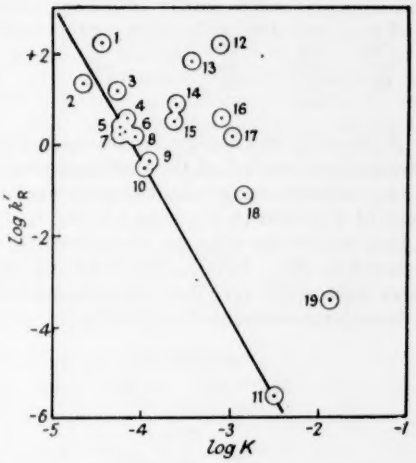



FIG. 3. *Plot of the logarithms of the specific rate constants* $(k'_R)$ *for the rearrangements of* CHMe:CH·CHX·OH *in* 60% *aqueous dioxan against the logarithms of the dissociation constants* $(k)$ *of* X·$CO_2$H *in water.* X = (1) p-*methoxyphenyl*, (2) *propenyl*, (3) p-*tolyl*, (4) 2-*naphthyl*, (5) m-*tolyl*, (6) *phenyl*, (7) *vinyl*, (8) p-*fluorophenyl*, (9) p-*chlorophenyl*, (10) p-*bromophenyl*, (11) *acetyl*, (12) 2-*furyl*, (13) 2-*thienyl*, (14) 9-*anthryl*, (15) 1-*naphthyl*, (16) o-*tolyl*, (17) 9-*phenanthryl*, (18) *hex*-1-*ynyl*, (19) *ethynyl*.

the straightforward relationship held. The four "abnormal" benzenoid groups all contain *o*-substitutents or their equivalent; evidently, steric inhibition to electronic interaction between X and the side-chain reduces the stability of the carboxylate ions X·$CO_2^-$ relative to the undissociated acids X·$CO_2$H much more seriously than it does that of oxonium ions (*e.g.*, I*a*) relative to the alcohols (*e.g.*, I). This is quite understandable, since charge-resonance involving X will be much more marked in the carboxylate ions than in the oxonium ions, and analogous steric "*ortho*"-effects have been observed in other reactions (Hammett, *loc. cit.*; Burkhardt *et al.*, *loc. cit.*). The deviation from the linear relation of the five-membered heterocyclic and acetylenic derivatives similarly indicates that these groups, unlike ethylenic and acetyl groups, do not readily partake in charge-resonance involving the accommodation of a negative charge, in agreement with previous conclusions (Braude and Stern, *loc. cit.*, 1947; Braude and Fawcett, *loc. cit.*, 1952).

*The Cyclisation Reaction.*—Although cyclisation reactions of the type (II) ⟶ (III) are well known (for references, see Part II, *loc. cit.*), hardly any kinetic measurements have been reported. In the case of saturated γ-hydroxy-ketones, the furan derivatives have been shown to exist in equilibrium with the open-chain forms (cf. Hurd and Saunders, *J. Amer. Chem. Soc.*, 1952, **74**, 5324). In the present system, cyclisation is essentially complete (>95%) under the conditions examined. At the higher concentrations used in preparative experiments (Part III, *loc. cit.*), cyclisation is accompanied by extensive self-etherification of the dihydrohydroxyfuran (III); this is probably absent under the

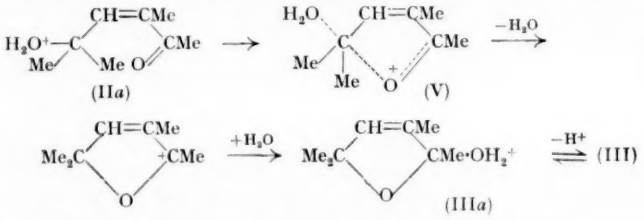
conditions of the kinetic runs, since the rate of etherification in analogous cases decreases rapidly with concentration (cf. Braude, Fawcett, and Newman, *J.*, 1950, 793). In any case, etherification will have no effect on the measured rates of cyclisation, since the extinction coefficients of (III) and the corresponding diether will be practically identical.

The cyclisation of (II), like the anionotropic rearrangement by which (II) is formed, is acid-catalysed, but exhibits a very different dependence on medium composition. The rate constants are rather more than doubled on increase of the acid concentration from 0·1 to 0·2M and *increase* markedly with decreasing water concentration; the relative rates in 40, 60, and 80% aqueous dioxan are in the ratio 1 : 3 : 10 (Table 3). The energies of activation for 40 and 60% aqueous dioxan–0·1M-hydrochloric acid are *ca.* 30 and 23 kcal./mole, respectively; as in the rearrangement of (I) (see above), and no doubt owing to the same cause, the rate constants at 95° fall considerably below the plots of log $k$ against $1/T$, and were neglected.

TABLE 3. *First-order rate constants* ($k_0$ *in min.*$^{-1}$) *for the cyclisation* (II) ⟶ (III) *in aqueous dioxan–hydrochloric acid. Keto-alcohol concentration* ca. 0·0043 *mole/l. throughout* (*for meaning of symbols, see Table* 1).

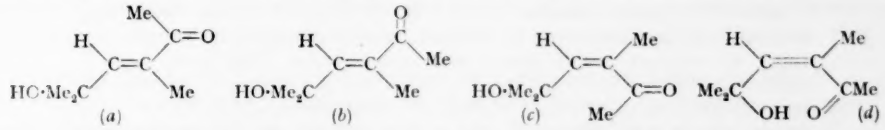
| $t$ | $c_A$ | $10^4k_c$ (40% dioxan) | $10^4k_c$ (60% dioxan) | $10^4k_c$ (80% dioxan) | $t$ | $c_A$ | $10^4k_c$ (40% dioxan) | $10^4k_c$ (60% dioxan) |
|---|---|---|---|---|---|---|---|---|
| 75° | 0·1 | 16·5 | 68 | — | 90° | 0·1 | 97 | 235 |
| 80 | 0·1 | 30 | 115 | — | | 0·2 | — | 680 |
| 85 | 0·1 | 51 | 170 | 2030 | 95 | 0·1 | 105 | 255 |
| | 0·2 | — | 515 | — | | | | |

A plausible mechanism for the cyclisation involves the oxonium ion (II*a*) which is the intermediate product of the rearrangement. The next step will be an electrophilic attack at the carbonyl oxygen by the $\gamma$-carbon atom, rendered partially positive by the attachment of a proton to the neighbouring hydroxyl group. The $\gamma$-carbon atom and the two oxygen atoms can take up an approximately linear arrangement in the transition state, depicted in (V). Finally, the resulting cyclic carbonium ion rapidly captures a solvent water molecule to give the conjugate acid (III*a*) of the dihydrohydroxyfuran, or a dihydrohydroxyfuran molecule to give the corresponding diether (cf. Part III, *loc. cit.*).




It will be noted that, independently of the details of the intermediate steps, the cyclisation requires a *cis*-arrangement of the –COMe and –$CMe_2$·OH groups about the ethylenic double bond. The actual orientation of the groups in the keto-alcohol (II), as isolated, is not certain, but it is clear that the geometrical isomers will be readily interconvertible in acid solution owing to the presence of a small concentration of oxonium ions formed by addition of a proton at the *carbonyl*-oxygen atom and charge-resonance in the resulting C=C–C=OH$^+$ ⟷ $^+$C–C=C–OH system. Now, there are four possible arrangements of the *cis*- and *trans*-isomers in which the conjugated system is uniplanar, namely the *trans-s-trans* (*a*), *trans-s-cis* (*b*), *cis-s-trans* (*c*), and *cis-s-cis* (*d*) conformations. Of these, (*d*) is obviously the most conducive to cyclisation, while (*a*) is probably the most stable thermodynamically, since the transoid arrangement of a conjugated system is normally favoured (Aston *et al.*, *J. Chem. Phys.*, 1946, **14**, 67; Braude *et al.*, *J.*, 1949, 1890; 1952, 1419), and since uniplanarity in (*c*) is, moreover, opposed by steric hindrance. If the *trans-s-trans*-conformation (*a*) predominates in solution, the rate of cyclisation will depend directly on the small equilibrium concentration of the *cis-s-cis* conformation (*d*), and the very marked accelerating effect of decreasing the water content of the medium may be explained in the

following way. In the more aqueous solvent, the acetyl group will be extensively solvated by water molecules (cf. p. 3140), and conformation (*a*) will be stabilised additionally with respect to (*d*). As the water concentration is decreased, however, external solvation of the acetyl group will become incomplete and the *cis-s-cis* conformation (*d*) will gain in




relative stability, since the distance between the hydroxyl-hydrogen atom and the carbonyl-oxygen atom is here sufficiently small for *internal* solvation of the acetyl group. Thus, the proportion of (*d*) and the rate of cyclisation will increase with decreasing water content of the medium. This interpretation is also in accord with the marked decrease in the energy of activation of the cyclisation on changing from 40% to 60% dioxan.

## Experimental

The keto-alcohols were those described in Part III (*loc. cit.*). The reaction media described as "40, 60, and 80%" aqueous dioxan were made up by mixing 40·5, 60·8, and 81·0 ml. of dioxan with appropriate volumes of aqueous hydrochloric acid and water to give 100 ml. of solution. The kinetic measurements were carried out by the method previously described, with a Beckman photo-electric spectrophotometer, Model DU (cf. Braude and Fawcett, *J.*, 1950, 800). In the rearrangement of (I), where the first-order rate constants decrease as the reaction progresses, the plots of $k$ against time were approximately linear and the values of $k$ for $t = 0$ were obtained graphically by extrapolating the plots. The values thus obtained were reproducible within ±2%. Most of the data in Tables 1 and 3 are based on duplicate runs. Six typical runs are reproduced below.

(i) Rearrangement of (I) in 40% dioxan–0·1M-HCl, at 75°. $c_{ROH} = 0·00607$.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 32·4 | 44·0 | 54·2 | 63·7 | 74·2 | 85·2 | 95·7 | 107 | 119 | — |
| $10^{-1}$ ε (2290 Å) | 93 | 171 | 198 | 220 | 238 | 260 | 271 | 289 | 303 | 332 | 1130 |
| $10^4k$ (min.$^{-1}$) ... | 27·0 * | 24·3 | 24·3 | 24·4 | 34·7 | 23·5 | 22·2 | 21·9 | 21·1 | 21·9 | — |

(ii) Rearrangement of (I) in 60% dioxan–0·1M-HCl, at 75°. $c_{ROH} = 0·00608$.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 16·1 | 20·0 | 24·2 | 30·3 | 34·9 | 39·6 | 47·7 | 52·2 | 56·3 | — |
| $10^{-1}$ ε (2290 Å) | 93 | 116 | 117 | 121 | 122 | 133 | 134 | 137 | 140 | 142 | 1130 |
| $10^4k$ (min.$^{-1}$) ... | 16·9 * | 15·3 | 13·8 | 12·2 | 10·0 | 11·8 | 11·1 | 9·8 | 9·4 | 9·2 | — |

(iii) Rearrangement of (I) in 40% dioxan–0·1M-HCl, at 85°. $c_{ROH} = 0·00565$.

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 5·9 | 8·9 | 12·2 | 13·9 | 15·5 | 17·4 | 19·2 | 21·1 | — |
| $10^{-1}$ ε (2290 Å) | 99 | 142 | 155 | 182 | 192 | 203 | 212 | 221 | 228 | 1130 |
| $10^4k$ (min.$^{-1}$) ... | 74·5 * | 74·5 | 65·6 | 69·5 | 68·6 | 68·7 | 66·6 | 66·1 | 64·6 | — |

* Extrapolated.

(iv) Cyclisation of (II) in 40% dioxan–0·1M-HCl, at 75°. $c_{ROH} = 0·00437$.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 160 | 230 | 284 | 299 | 337 | 372 | | 2800 |
| $10^{-1}$ ε (2290 Å) | 983 | 825 | 757 | 629 | 684 | 673 | 633 | | 242 |
| $10^4k$ (min.$^{-1}$) ... | — | 14·9 | 16·5 | 17·6 | 17·2 | 16·0 | 17·1 | (Mean) | 16·5 |

(v) Cyclisation of (II) in 60% dioxan–0·1M-HCl, at 75°. $c_{ROH} = 0·00325$.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 51·2 | 58·7 | 76·4 | 85·5 | 94 | 103 | | 990 |
| $10^{-1}$ ε (2290 Å) | 1020 | 764 | 710 | 655 | 614 | 593 | 563 | | 124 |
| $10^4k$ (min.$^{-1}$) ... | — | 64 | 66 | 71 | 71 | 69 | 68 | (Mean) | 68 |

(vi) Cyclisation of (II) in 40% dioxan–0·1M-HCl, at 85°. $c_{ROH} = 0·00458$.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (min.) ... | 0 | 49 | 65 | 72 | 80 | 88 | 101 | 113 | 144 | | 1400 |
| $10^{-1}$ ε (2290 Å) | 1040 | 853 | 807 | 788 | 753 | 747 | 714 | 687 | 617 | | 226 |
| $10^4k$ (min.$^{-1}$) ... | — | 51·7 | 49·9 | 50·7 | 53·3 | 50·0 | 50·1 | 49·8 | 50·2 | (Mean) | 50·7 |

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## 626. *The Synthesis and Prototropic Rearrangement of 4-Hydroxyhept-5-en-3-one.*

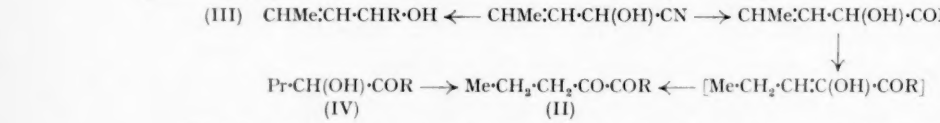
By E. A. Braude and C. J. Timmons.

4-Hydroxyhept-5-en-3-one, CHMe:CH·CH(OH)·COEt, has been synthesised from crotonaldehyde cyanohydrin and ethylmagnesium bromide and found to undergo double prototropic rearrangement with great ease to heptane-3 : 4-dione, Me·$CH_2$·$CH_2$·CO·COEt. The reaction of crotonaldehyde cyanohydrin with other ethyl- or with methyl-magnesium halides results predominantly in replacement of, rather than addition to, the cyano-group, giving the alcohols CHMe:CH·CHR·OH (R = Me or Et).

The ultra-violet light absorption properties of α-keto-alcohols and their derivatives are briefly discussed and appreciable spectral interaction is noted between the unconjugated ethylenic and carbonyl chromophores in the C=C–C–C=O system.

The work of Heilbron, Jones, Smith, and Weedon (*J.*, 1946, **54**; cf. Braude and Timmons, *J.*, 1953, 3131) leads to the conclusion that βγ-ethylenic α-hydroxy-ketones containing the system C=C·CH(OH)·C=O (*e.g.*, I) are converted with great ease into α-diketones (*e.g.*, II) by double prototropic rearrangement. As systems of this type have only been postulated as probable intermediates, but have not actually been isolated, it was of interest to synthesise a keto-alcohol such as (I) and confirm the occurrence of the expected reaction.

An obvious route to (I) is by the reaction of Grignard reagents with crotonaldehyde cyanohydrin. The addition of Grignard reagents to the cyano-group of aldehyde cyanohydrins has been described in a number of cases (cf. Gauthier, *Compt. rend.*, 1911, **152**, 1100; Tiffeneau and Levy, *Bull. Soc. chim.*, 1925, **37**, 1247; Willstaedt, *Svensk Kem. Tidskr.*, 1941, **53**, 416; Ruggli and Hegedüs, *Helv. Chim. Acta*, 1942, **25**, 1285). On the other hand, ketone cyanohydrins, originally claimed to react in an analogous manner (Gauthier, *Compt. rend.*, 1911, **152**, 1259), were later shown to yield tertiary alcohols by replacement of, instead of addition to, the cyano-group (Geurden, *Bull. Soc. chim. Belg.*, 1926, **35**, 253; Khaletskii, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2854). Crotonaldehyde cyanohydrin and alkylmagnesium halides in ether reacted in both ways, and the proportion of replacement and addition was found to depend in a somewhat unexpected manner on the nature of the alkyl and the halide groups (Table 1). With MeMgBr, MeMgI, EtMgCl, and EtMgI replacement predominates, whereas with EtMgBr the keto-alcohol (I; R = Et), formed by addition, is the main isolatable product. In each case, the keto-alcohol was accompanied by some of the corresponding saturated diketone (II), the expected product of double prototropic rearrangement. Higher-boiling materials were also formed, which were not investigated. In contrast to the comparatively low overall yields obtained from crotonaldehyde cyanohydrin, butyraldehyde cyanohydrin and ethylmagnesium bromide gave a 90% yield of the saturated keto-alcohol, 4-hydroxyheptan-3-one (IV; R = Et).




The keto-alcohols (I) and diketones (II) were isolated in the pure state only from the reaction with ethylmagnesium bromide, but the proportions of the three main products could be estimated spectrometrically in each case, on the assumption that the characteristic ultra-violet and visible absorptions of the methyl and ethyl homologues are identical. The keto-alcohols (I) exhibit well-defined low-intensity bands at 2810 Å ($\varepsilon \sim 300$) associated with the C(OH)·CO grouping, while the diketones (II) exhibit bands near 4300 Å ($\varepsilon \sim 20$) characteristic of the CO·CO grouping. The proportion of the alcohols (III), which are optically transparent in these regions, was obtained by difference. The results are summarised in Table 1.

The alcohols (III) were identified by comparison with authentic specimens, prepared from crotonaldehyde and methyl- or ethyl-magnesium bromide, and by their *p*-nitrobenzoates and α-naphthylurethanes. It was suggested by Geurden and by Khaletskii (*locc. cit.*) that the formation of alcohols in the reaction of cyanohydrins with Grignard reagents involves decomposition of the cyanohydrin to the ketone or aldehyde, followed by normal addition to the carbonyl group. It seems far more probable, however, that a

TABLE 1. *Yields* (%) *of products from crotonaldehyde cyanohydrin and* RMgX.

| | MeMgBr | MeMgI | EtMgCl | EtMgBr | EtMgI |
|---|---|---|---|---|---|
| Alcohol (III) | 18 | 26 | 25 | 3 | 28 |
| Keto-alcohol (I) | 1 | 3 | 3 | 23 | 8 |
| Diketone (II) | 1 | 1 | 1 | 8 | 5 |
| Total | 20 | 30 | 29 | 34 | 41 |

direct nucleophilic replacement of the cyano-group occurs, which has been observed with some other nitriles (cf. Rabe and Pasternack, *Ber.*, 1913, **46**, 1026; Stevens, Cowan, and McKinnon, *J.*, 1931, 2568; Fuson, Emmons, and Tull, *J. Org. Chem.*, 1951, **16**, 648; Schultz, *J. Amer. Chem. Soc.*, 1952, **74**, 5793) and will be favoured by inductively electron-attracting substituents (such as OH).

Extensive fractionation of the products from the reaction with ethylmagnesium bromide gave the keto-alcohol 4-hydroxyhept-5-en-3-one (I; R = Et) and the diketone, heptane-3 : 4-dione (II; R = Et). Heptane-3 : 4-dione was isolated through the bisulphite derivative and was characterised by the phenylosazone, bis-2 : 4-dinitrophenylhydrazone, and quinoxaline, identical with the derivatives of an authentic sample of the diketone prepared by the oxidation of 3-hydroxyheptan-2-one (IV; R = Et) with lead tetra-acetate. 4-Hydroxyhept-5-en-3-one was characterised by a mono-2 : 4-dinitrophenylhydrazone. On treatment with phenylhydrazine in the presence of acetic acid, it afforded the phenylosazone of heptane-3 : 4-dione, evidently formed by prototropic rearrangement under the mildly acid conditions. The ready occurrence of prototropic rearrangement in systems of the type C=C–CR(OH)–C=O, where R = H, is thus confirmed. It has been shown (Braude and Timmons, *loc. cit.*) that anionotropy in systems of this type can be effected if prototropy is blocked by suitable alkyl substitution and it is highly probable that both types of reaction proceed through the same intermediate oxonium ion C=C–CR($OH_2^+$)–X, formed by reversible addition of a proton to the hydroxyl group. If R = Me, anionotropy takes place, though it is greatly retarded when X contains the strongly electron-attracting carbonyl group. If R = H, prototropy becomes possible and separation of R as a proton will be assisted by the adjacent positive change in the oxonium ion. In this case, the mode of rearrangement is controlled by the nature of the substituent X; anionotropy predominates when X is either an electron-donating or even a moderately electron-attracting group such as –C≡CH (Braude, *Quart. Reviews*, 1950, **4**, 404), but only prototropy is observed when X is a very strongly electron-attracting group such as –COMe.

Ultra-violet light absorption data for the α-keto-alcohols (I) and (IV) and for some derivatives and related compounds are given in Table 2. The three main generalisations which emerge are: (1) an α-hydroxyl or α-alkoxyl substituent displaces the low-intensity *R*-band near 2800 Å associated with an isolated carbonyl group towards longer wave-lengths by *ca.* 50 Å, (2) an α-hydroxyl substituent has the opposite effect on the long-wave-length bands of the corresponding 2 : 4-dinitrophenylhydrazones which are displaced by *ca.* 50 Å to shorter wave-lengths, and (3) a βγ-ethylenic bond causes a four- to ten-fold increase in the intensity of the 2800-Å band associated with the carbonyl group.

The bathochromic effects of α-hydroxyl as well as other saturated substituents in the R–C–C=O system have been noted previously (cf. Rice, *J. Amer. Chem. Soc.*, 1920, **42**, 725; Herold, *Z. physikal. Chem.*, 1932, **18**, *B*, 265; Lowry and Lishmund, *J.*, 1935, 1313); their interpretation in terms of the forbidden transition of oxygen *p* electrons to the anti-bonding π orbital thought to be responsible (McMurry, *J. Chem. Physics*, 1941, **9**, 231) for the 2800-Å bands is not very clear. The hypsochromic effect of α-hydroxyl groups in hydrazones has also been observed in steroid derivatives (Fleisher and Kendall, *J. Org.*

*Chem.*, 1951, **16**, 566), and similar effects are found with acetoxyl, carboxyl,* and halogeno-substituents (Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331), whereas methyl groups have bathochromic effects (Braude and Jones, *J.*, 1945, 498). The excited state of the electronic transition giving rise to the characteristic band of the 2 : 4-dinitrophenylhydrazones is polarised in the sense $CX{-}C{=}N{-}NH^{+}{=}C_6H_4{=}N(O){-}O^{-}$ and the hypsochromic

TABLE 2. *Ultra-violet absorption of α-keto-alcohols and derivatives.*

| | Ketone * | | 2 : 4-Dinitrophenylhydrazone † | |
|---|---|---|---|---|
| | $\lambda_{max.}$ (Å) | ε | $\lambda_{max.}$ (Å) | ε |
| $Pr^{n}$·COMe | 2770 | 21 [1] | 3650 | 22,000 |
| $Pr^{i}$·COMe | 2800 | 21 [1] | — | — |
| $Me_2C(OH)$·COMe | 2810, 2910 | 25 | 3550 | 23,000 |
| $Pr^{n}$·CH(OH)·COEt | 2820, 2910 | 40 | 3590 | 26,000 |
| $Pr^{i}$·CH(OH)·$COPr^{i}$ | 2880 | 30 | 3600 | 20,000 |
| Me·C(OMe)$_2$·COMe | 2960 | 25 [2] | — | — |
| CHMe:CH·CH(OH)·COEt | 2810, 2900 | 300 | 3530 | 31,000 |
| $CMe_2$:CH·CMe(OH)·COMe | 2810 | 230 [2] | 3580 | 23,000 [2] |
| $CH_2$:CHMe·$CH_2$·COMe | 2900 | 80 [3] | — | — |
| Ph·$CMe_2$·COMe | 2900 | 160 [4] | — | — |

* In ethanol. † In chloroform.

[1] Rice, *loc. cit.* [2] Braude and Timmons, *J.*, 1953, 3131. [3] Gray, Rasmussen, and Tunnicliff, *J. Amer. Chem. Soc.*, 1947, **69**, 1630 (octane solution). [4] Kumler *et al.*, *loc. cit.*

displacements are ascribable to the counter-polarisation $X^{-}\ C{=}C{-}N^{+}$ due to hyperconjugative electron attraction which will be effective in an allowed transition. Such interaction is analogous to that observed in allylic (X–C–C=C) and similar systems (Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1951, 2085; Armitage and Whiting, *J.*, 1952, 2005), although in these cases the displacements are uniformly bathochromic because the transition will be facilitated by hyperconjugative polarisation in either direction, *e.g.*, $X^{-}\ C{=}C{-}C^{+}$ or $X^{+}\ C{=}C{-}C^{-}$.

The effect of a βγ-ethylenic bond in the C=C–C–C=O systems provides an interesting example of interaction between unconjugated chromophores (Braude, *J.*, 1949, 1902) and is reminiscent of the strong intensification of the carbonyl band observed in the α-phenyl ketone system Ph–C–C=O (Kumler, Strait, and Alpen, *J. Amer. Chem. Soc.*, 1950, **72**, 1463, 4558). It may be represented as a hyperconjugative interaction of the type $C{=}C{-}C{-}C{=}O \longleftrightarrow C{=}C{-}C^{+}\ C{\equiv}O^{-} \longleftrightarrow C^{+}{-}C{=}C\ C{\equiv}O^{-}$.

## EXPERIMENTAL

M. p.s marked (K) were determined on a Kofler block and are corrected. Other m. p.s are uncorrected (sealed capillary). Light absorption data are only given when not included in Table 2.

*4-Hydroxyhept-5-en-3-one* (I; R = Et).—Crotonaldehyde cyanohydrin (97 g.; b. p. 95°/5 mm.; cf. Moureu, Murat, and Tampier, *Bull. Soc. chim.*, 1921, **29**, 29) in ether (300 ml.) was added during 2 hr. to a stirred solution of ethylmagnesium bromide (from Mg, 72 g.) in ether (1 l.) under nitrogen. After 15 hr., saturated aqueous ammonium chloride (700 g.) was added, and the ethereal layer was separated, dried ($Na_2SO_4$), and distilled. A total of 40 g. (31%) of products boiling in the range 50—85°/18 mm. was obtained, which had $n_D^{23}$ 1·425—1·442, $\lambda_{max.}$ 2600 ($E^{1\%}_{1\,cm.}$ 20) and 4300 Å ($E^{1\%}_{1\,cm.}$ 0·6), and consisted of a mixture of (i) 4-hydroxyhept-5-en-3-one (*ca.* 70%), (ii) heptane-3 : 4-dione (*ca.* 20%), and (iii) hex-4-en-3-ol (*ca.* 10%), which were separated as follows:

(i) Extensive fractionation afforded pure *4-hydroxyhept-5-en-3-one* as a colourless oil, b. p. 58—59°/0·7 mm., 78—79°/12 mm., $n_D^{16}$ 1·4532 (Found: C, 65·7; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). The 2 : 4-*dinitrophenylhydrazone* separated from aqueous methanol in yellow needles, m. p. 93—94° (Found: C, 50·9; H, 5·0; N, 18·2. $C_{13}H_{16}O_5N_4$ requires C, 50·7; H, 5·2; N, 18·2%).

Treatment of the keto-alcohol (1 g.) with phenylhydrazine hydrochloride (3·6 g.) and sodium

* Thus, pyruvic acid 2 : 4-dinitrophenylhydrazone shows $\lambda_{max.}$ 3510 Å (ε 24,000) in $CHCl_3$. The value 3600 Å given earlier (Braude and Jones, *loc. cit.*) is incorrect; we are indebted to Professor H. Reich (Utah) for drawing our attention to this error.

acetate (2·7 g.) in 50% aqueous ethanol at 80° (2 hr.) gave heptane-3 : 4-dione phenylosazone, m. p. 106—107°, undepressed on admixture with the sample described below.

(ii) The lower-boiling fractions were extracted with aqueous sodium hydrogen sulphite, and the aqueous extract was concentrated, acidified with hydrochloric acid, and steam-distilled, giving heptane-3 : 4-dione, b. p. 92°/102 mm., $n_D^{19}$ 1·4118 (Found : C, 65·3; H, 9·6. Calc. for $C_7H_{12}O_2$ : C, 65·6; H, 9·4%) (Favorskii and Venus-Danilova, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 369, give b. p. 58—61°/25 mm.). It formed a bis-2 : 4-dinitrophenylhydrazone, m. p. 263—264° and a phenylosazone, m. p. 106—107°, undepressed on admixture with the authentic specimens described below.

(iii) Treatment of the residual low-boiling fractions from (ii) with *p*-nitrobenzoyl chloride in pyridine gave the *p*-nitrobenzoate, m. p. and mixed m. p. 41—43°, of hex-2-en-4-ol. An authentic sample of the alcohol was prepared from crotonaldehyde and ethylmagnesium bromide and had b. p. 62°/30 mm., $n_D^{17}$ 1·4368 (von Auwers and Westermann, *Ber.*, 1921, **54**, 2996, give b. p. 59°/27 mm., $n_D^{23}$ 1·4329). The p-*nitrobenzoate* crystallised from aqueous methanol in plates, m. p. 42—44° (Found : C, 62·3; H, 6·2; N, 5·7. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·1; N, 5·6%).

Seven similar runs with some variations in the conditions of the Grignard addition gave total yields of 20—40% and some differences in the composition of the products, but no definite correlation was established.

4-*Hydroxyheptan*-3-*one* (IV; R = Et).—Butyraldehyde cyanohydrin (38 g.; b. p. 92°/1 mm., $n_D^{16}$ 1·4225; Ultée, *Rec. Trav. chim.*, 1909, **28**, 252) was added to ethylmagnesium bromide (from Mg, 29 g.), and the product isolated as above, giving 4-hydroxyheptan-3-one as a colourless liquid (44 g., 91%), b. p. 71°/11 mm., $n_D^{19}$ 1·4297 (Found : C, 64·8; H, 10·6%; *M*, in camphor, 135; active H, 1·01 atoms. Calc. for $C_7H_{14}O_2$ : C, 64·6; H, 10·8%; *M*, 130). The semicarbazone separated from water in plates, m. p. 115° (Found : C, 51·6; H, 9·2; N, 22·5. Calc. for $C_8H_{17}O_2N_3$ : C, 51·3; H, 9·2; N, 22·5%) (Favorskii and Venus-Danilova, *loc. cit.*, give b. p. 74—75°/18 mm. for the keto-alcohol and m. p. 121—122° for the semicarbazone). The 2 : 4-*dinitrophenylhydrazone* separated from aqueous methanol in yellow needles, m. p. 96° (Found : C, 50·6; H, 6·1; N, 18·3. $C_{13}H_{18}O_5N_4$ requires C, 50·3; H, 5·9; N, 18·1%). Treatment of the keto-alcohol with phenylhydrazine acetate gave the phenylosazone, m. p. 107°, of heptane-3 : 4-dione, undepressed on admixture with the sample described below.

*Heptane*-3 : 4-*dione* (II; R = Et).—(*a*) 4-Hydroxyheptan-3-one (3·9 g.), lead tetra-acetate (13·4 g.), and anhydrous ether (90 ml.) were heated under reflux for 5 hr. Isolation of the product by means of sodium hydrogen sulphite as above gave the dione (2 g.), b. p. 98—99°/105 mm., $\lambda_{max.}$ 2640 and 4300 Å (ε 35 and 21) in hexane, $\lambda_{max.}$ 2670 and 4210 Å (ε 35 and 16) in EtOH (Found : C, 65·3; H, 9·6. Calc. for $C_7H_{12}O_2$ : C, 65·6; H, 9·4%) (Favorskii and Venus-Danilova, *loc. cit.*, give b. p. 58—61°/25 mm.). The *phenylosazone* separated from aqueous methanol in yellow plates, m. p. 107°, $\lambda_{max.}$ 3530 Å (ε 51,000) in EtOH (Found : C, 73·9; H, 7·8; N, 18·3. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8; N, 18·2%). The *bis*-2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene–methanol or aqueous dioxan in red needles, m. p. 264° (K), $\lambda_{max.}$ 2600, 2800, and 3980, $\lambda_{infl.}$ 4350 Å (ε 38,000, 28,000, 52,000, and 45,000) in $CHCl_3$ (Found : C, 47·1; H, 4·4; N, 22·9. $C_{19}H_{20}O_8N_8$ requires C, 46·7; H, 4·1; N, 22·9%). The *quinoxaline* derivative separated from aqueous methanol in buff crystals, m. p. 44° (K) (Found : N, 14·0. $C_{13}H_{16}N_2$ requires N, 14·0%).

(*b*) 4-Hydroxyhept-5-en-3-one (1 g.) was added to potassium dichromate (0·4 g.) in sulphuric acid (10%; 20 ml.). After 1 hr., the mixture was extracted with ether. Evaporation gave heptane-3 : 4-dione (0·6 g.) which on treatment with Brady's reagent gave an immediate precipitate of the bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 259°.

*Reactions of Alkylmagnesium Halides with Crotonaldehyde Cyanohydrin.*—The reactions were performed as in the case of ethylmagnesium bromide, and the compositions of the products were estimated spectrometrically as described above. Only the principal products were isolated.

(*a*) Methylmagnesium bromide gave pent-3-en-2-ol (14 g., 18%), b. p. 75°/180 mm., $n_D^{19}$ 1·4305 (*p*-nitrobenzoate, m. p. and mixed m. p. 54—57°). An authentic sample prepared from crotonaldehyde had b. p. 120°/760 mm., $n_D^{15}$ 1·4311 (Auwers and Westermann, *loc. cit.*, give b. p. 64°/62 mm., $n_D^{18}$ 1·4282). The p-*nitrobenzoate* crystallised from aqueous methanol in plates, m. p. 54—55° (Found : N, 5·5. $C_{12}H_{13}O_4N$ requires N, 5·6%). The α-*naphthylurethane* separated from aqueous methanol in needles, m. p. 110—111° (K) (Found : C, 75·2; H, 6·6; N, 5·8. $C_{16}H_{17}O_2N$ requires C, 75·0; H, 6·7; N, 5·5%).

(*b*) Methylmagnesium iodide gave pent-3-en-2-ol (18 g., 26%), b. p. 65°/80 mm., $n_D^{17}$ 1·4297, identified by the *p*-nitrobenzoate, m. p. 54—55°, and α-naphthylurethane, m. p. 108—110°.

(*c*) Ethylmagnesium chloride gave hex-4-en-3-ol (25 g., 28%), b. p. 135—138°, $n_D^{22}$ 1·4312,

identified as the *p*-nitrobenzoate, m. p. and mixed m. p. 42—44°. Heptane-3 : 4-dione was identified in the crude product as the bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 260—263°.

(*d*) Ethylmagnesium iodide gave a mixture of products (total 34 g., 41%; see Table 1) in which hex-4-en-3-ol was identified by the *p*-nitrobenzoate, m. p. 43—44°, and heptane-3 : 4-dione by the bis-2 : 4-dinitrophenylhydrazone, m. p. 260°.

*iso*Butyroin, prepared by the method of Bouveault and Locquin (*Bull. Soc. chim.*, 1906, **35**, 642), had b. p. 82·5°/26 mm., 182°/759 mm., $n_D^{28}$ 1·4232 (Bouveault and Locquin, *loc. cit.*, give b. p. 83°/26 mm.). The *toluene*-p-*sulphonate* crystallised from aqueous methanol in colourless needles, m. p. 49—50° (K) (Found: C, 60·5; H, 7·7; S, 10·6. $C_{15}H_{22}O_4S$ requires C, 60·4; H, 7·4; S, 10·7%). The hydroxy-ketone with 2 : 4-dinitrophenylhydrazine sulphate in aqueous ethanol during 5 days slowly gave a precipitate, which was separated by chromatography on alumina with benzene and chloroform into *isobutyroin* 2 : 4-*dinitrophenylhydrazone* (α-*form*) (10%) which crystallised from aqueous methanol in yellow needles, m. p. 98—101° (K) (Found: C, 52·8; H, 6·4; N, 17·3. $C_{14}H_{20}O_5N_4$ requires C, 51·9; H, 6·2; N, 17·2%), and a β-*form* (50%) which crystallised from aqueous methanol in orange prisms, m. p. 145—147° (K), $\lambda_{max.}$ 3730 Å (ε 22,500) in $CHCl_3$ (Found: C, 52·1; H, 6·4; N, 17·2%).

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## 627. *Organosilicon Compounds. Part VI.* The Kinetics of the Acid-catalysed Cleavage of* p-*Methoxyphenyltrimethylsilane.*

By C. Eaborn.

The rates of cleavage of the Si–C bond of *p*-methoxyphenyltrimethylsilane by hydrochloric and perchloric acid in aqueous methanol, and by the former acid in aqueous dioxan have been studied spectrophotometrically. The reaction is of first order in the silane, and for a given solvent the rate of reaction is governed by the acidity function of the system; this indicates the rapid formation of an intermediate, probably one in which a proton is attached to the aromatic carbon atom joined to silicon. Changes of rate caused by variation of the water content of the solvent suggest that nucleophilic attack on silicon may be involved in the rate-determining decomposition of the intermediate.

Aromatic groups are readily cleaved from silicon by acids, particularly by concentrated sulphuric acid (*e.g.*, Kipping, *J.*, 1907, 211; 1921, 647). The effects of nuclear substituents on the ease of cleavage appear to parallel those on ease of electrophilic aromatic substitution, since the Si–$C_6H_4$·$NH_2$-*p* link is readily, and the Si–$C_6H_4$·$NH_2$-*m* link much less readily, cleaved by acids, while the Si–$C_6H_4$·$NO_2$ link, whether *meta* or *para*, is very stable to acids (Kipping and Cusa, *J.*, 1935, 1088). Furthermore, for cleavage by hydrogen chloride in glacial acetic acid the ease of removal of groups from silicon is in the order, 2-thienyl > *p*-methoxyphenyl and *p*-dimethylaminophenyl > *p*-tolyl > phenyl > *p*-chlorophenyl (Gilman and Marshall, *J. Amer. Chem. Soc.*, 1949, **71**, 2066). *p*-Methoxyphenyltrimethylsilane is now found to be cleaved much more easily than trimethylphenylsilane in aqueous-methanolic hydrochloric acid.

*Kinetics in Aqueous Methanol.*—The overall course of the acid-catalysed cleavage of *p*-methoxyphenyltrimethylsilane is represented by

$$p\text{-}Me_3Si\cdot C_6H_4\cdot OMe + ROH \xrightarrow{H^+} Me_3Si\cdot OR + C_6H_5\cdot OMe$$

(R = Me or H). The silanol or silicon ester is quickly converted into hexamethyldisiloxane. In 9 vol.-% of water in methanol, with hydrochloric acid as catalyst, the reaction is of first order in *p*-methoxyphenyltrimethylsilane throughout a run, and the first-order constant is independent of the initial concentration of the silane. As the concentration of acid is

* Part V, *J.*, 1953, 494.

increased from 0·04 to 1·1M the rate constant, $k$, increases rapidly, and the variation can be represented approximately by a relation of the form $k = k'[HCl]^{1·67}$ over the range 0·2—0·7M, or by $k = k''[HCl] + k''[HCl]^2/3$ over the range 0·1—0·8M. These equations fail to keep pace with the rate increase at higher acid concentrations.

With perchloric acid as catalyst the rates are higher than for hydrochloric acid at corresponding concentrations, and the rate rises even more rapidly with increasing acid concentration. This indicates that the rate-equation does not, in fact, involve a square term in acid, for while chloride ion could conceivably be concerned in nucleophilic attack in a transition state in which a proton makes electrophilic attack, giving rise to such a term, the weakly nucleophilic perchlorate ion is very unlikely to participate in this way.

The explanation of the results emerged when the acidity functions $H$ (Braude, *J.*, 1948, 1971) of the reaction media were determined, for a plot of log $k$ against $H$ is a straight line of unit slope over the range of hydrochloric acid concentrations studied, as shown in the following table

Solvent : 9 vol.-% water in methanol. Temp. 49·7°.

| [HCl],† M | 11·68 | 7·65 | 6·43 | 5·74 | 4·27 | 3·38 | 2·31 | 1·08 | 0·498 |
|---|---|---|---|---|---|---|---|---|---|
| $10^2k$, min.$^{-1}$ | 6·78 | 2·25 | 1·75 | 1·41 | 0·836 | 0·598 | 0·329 | 0·138 | 0·42 |
| $-H$ | 0·220 | 0·666 | 0·815 | 0·888 | 1·113 | 1·257 | 1·484 | 1·911 | — |
| $-(\log k - H)$ | 0·95 | 0·98 | 0·94 | 0·96 | 0·97 | 0·97 | 1·00 | 0·96 | — |

† This refers to the concentration of aqueous acid, 1 ml. of which was added to 10 ml. of methanolic solution of the silane.

Values of log $k - H$ are similarly constant for the perchloric acid solutions, and agree reasonably well with those for hydrochloric acid.

Solvent : As above. Temp. : 49·7°.

| [$HClO_4$],* M | 5·74 | 4·12 | 2·17 | 0·918 |
|---|---|---|---|---|
| $10^2k$, min.$^{-1}$ | 2·01 | 1·13 | 0·404 | 0·124 |
| $-H$ | 0·779 | 1·046 | 1·486 | 1·968 |
| $-(\log k - H)$ | 0·92 | 0·90 | 0·91 | 0·94 |

* See footnote to previous table.

Increase in the water content of the solvent from 9 to 27 vol.-% at a given concentration of hydrochloric acid slows the reaction, particularly at higher acid concentrations. The fall in rate is paralleled by a fall in the acidity function, but while the values of log $k - H$ remain satisfactorily constant as the acid concentration is varied in the 27% water–methanol, they are significantly greater than those in the less aqueous solvent. Water thus has an accelerating effect on the reaction which counteracts the fall in acidity function.

Solvent : 27 vol.-% of water in methanol. Temp. : 49·7°.

| [HCl],* M | 7·63 | 6·43 | 5·74 | 3·38 |
|---|---|---|---|---|
| $10^2k$, min.$^{-1}$ | 1·70 | 1·25 | 1·09 | 0·507 |
| $-H$ | 0·993 | 1·106 | 1·171 | 1·505 |
| $-(\log k - H)$ | 0·78 | 0·80 | 0·79 | 0·79 |

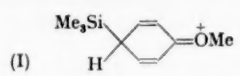
* See footnote to first table.

*Kinetics in Aqueous Dioxan.*—In 45·5 vol.-% water in dioxan the reaction is again of first order in *p*-methoxyphenyltrimethylsilane, and log $k - H$ is satisfactorily constant. When, however, the water content of the dioxan is increased over the range 8—25M(14—52 vol.-%) water the rate constant falls less rapidly than is required by the fall in $H$, so that the value of log $k - H$ increases. The values of log $k/[H_2O] - H$ are more nearly constant for 8—25M-water, while those of log $k/a_{H_2O} - H$ are satisfactorily constant over this range. and reasonably so over the whole range which could be studied.

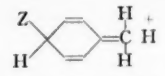
Solvent : Water–dioxan. Temp. : 49·7°.

| [$H_2O$], M | 8·12 | 10·11 | 12·64 | 15·17 | 20·22 | 25·28 | 26·90 | 28·77 | 25·28 | 25·28 | 25·28 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [HCl], M | 0·278 | 0·526 | 0·664 | 0·789 | 1·045 | 1·055 | 0·870 | 0·973 | 0·794 | 1·324 | 0·526 |
| $10^2k$, min.$^{-1}$ | 0·167 | 0·391 | 0·507 | 0·631 | 1·20 | 1·43 | 0·974 | 1·44 | 0·765 | 0·231 | 0·032 |
| $-H$ | 1·520 | 1·204 | 1·125 | 1·113 | 0·964 | 0·864 | 0·996 | 0·874 | 1·080 | 0·636 | 1·468 |
| $-(\log k) - H$ | 1·26 | 1·20 | 1·16 | 1·11 | 0·96 | 0·98 | 1·01 | 0·97 | 1·04 | 1·00 | 1·03 |
| $-(\log k/a_{H_2O}) - H$ | 2·40 | 2·41 | 2·43 | 2·45 | 2·40 | 2·50 | 2·55 | 2·54 | — | — | — |

*The Mechanism of the Reaction.*—Constancy of log $k - H$ for an acid-catalysed reaction is usually interpreted as indicating the existence of a fast reversible proton transfer from the solvent to the substrate before the rate-determining step (*e.g.*, Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 275; Braude and Stern, *J.*, 1948, 1982; Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3272). Since the effects of substituents on the acid cleavage of silicon–aryl bonds appear to parallel those on aromatic substitution, it seems probable that the *p*-methoxy-group activates through its $+E$ effect, so that an intermediate with a proton on the ether oxygen is unlikely to be effective in the cleavage reaction, but it cannot be finally rejected. An acceptable intermediate would be that having (as one mesomeric form) the structure (I). Ions of the analogous form (II) (with



(I)



(II)

resonance variations) have been postulated to exist in the complexes formed by aromatic hydrocarbons and hydrogen chloride in the presence of aluminium chloride ($Z = H^+$; Brown and Brady, *ibid.*, 1952, **74**, 3570) and by these hydrocarbons with hydrogen fluoride in presence of boron trifluoride ($Z = H$; McCaulay and Lien, *ibid.*, 1951, **73**, 2013), and as intermediates produced in the rate-determining step of aromatic nitration ($Z = NO_2$; Hughes, Ingold, and Reed, *J.*, 1950, 2400). The polarity $\overset{\delta+}{Si}–\overset{\delta-}{C}$ should facilitate the formation of the intermediate (I). If an intermediate of type (I) is general for acid-catalysed cleavage of silicon–aryl bonds, nuclear substituents which supply electrons to the carbon atom attached to silicon would increase the rate of cleavage by increasing the concentration of the intermediate, and the rules for aromatic substitution would apply to the cleavage. Furthermore, the particular effectiveness of concentrated sulphuric acid would be understandable, since the acidity functions of this medium are exceptionally high (Hammett, *op. cit.*, p. 268).

The protonated intermediate could decompose unimolecularly to form anisole and a siliconium ion, which would then quickly react with the solvent. In this case no molecule of water would be involved in covalency change in the transition state and log $k - H$ might be expected to remain reasonably constant as the water content of the medium is varied. However, the silicon atom is very susceptible to nucleophilic attack, and should be especially so in a positively charged complex. The reaction sequence could be:

$$p\text{-}Me_3Si\cdot C_6H_4\cdot OMe + H^+ \overset{\text{fast}}{\rightleftharpoons} p\text{-}Me_3Si\cdot\overset{+}{C}_6H_5\cdot OMe$$

$$p\text{-}Me_3Si\cdot\overset{+}{C}_6H_5\cdot OMe + H_2O \xrightarrow{\text{slow}} Me_3Si\cdot\overset{+}{O}H_2 + C_6H_5\cdot OMe$$

$$Me_3Si\cdot OH_2 \xrightarrow{\text{fast}} Me_3Si\cdot OH + H^+$$

Such a scheme is formally analogous to that postulated by Keading and Andrews (*J. Amer. Chem. Soc.*, 1952, **74**, 6189) for the acid hydrolysis of *p*-nitrobenzophenone diethyl ketal in aqueous ethanol, in which constancy of log $k/a_{H_2O} - H$, expected on the assumption of rate-determining attack of a water molecule on the oxonium salt of the ketal, was experimentally demonstrated. In the present case log $k/a_{H_2O} - H$ gives better constancy than log $k - H$ in aqueous dioxan, while log $k - H$ in 27% water–ethanol is higher than in the more weakly nucleophilic 9% medium. In the absence of evidence to the contrary it seems reasonable to suppose that nucleophilic attack on silicon is involved in the decomposition of the protonated intermediate, but no definite conclusion is possible.

*Acidity Functions, and the Activity of Water in Dioxan.*—The values of the acidity function of hydrochloric acid in aqueous methanol appear to be somewhat higher than in the corresponding ethanolic solutions (Braude and Stern, *J.*, 1948, 1976). The acidity functions of solutions of perchloric acid in 9% water–methanol are higher than those of hydrochloric acid of the same concentration, as is the case for more concentrated aqueous solutions (Hammett, *op. cit.*, p. 269).

Values of the activities of water in dioxan containing hydrochloric acid are not available. Since the mole fractions of hydrochloric acid present in the kinetic studies were relatively low, the activity coefficients of water in dioxan were used as an approximation. These were calculated from the partial vapour pressures of water in dioxan at 25° (listed by Hovorka, Schaefer, and Dreisbach, *ibid.*, 1936, **58**, 2264), according to the method of Butler, Thomson, and Maclennan (*J.*, 1933, 674), with the following results:

| Water, mole fraction | 0·1 | 0·2 | 0·3 | 0·4 | 0·5 | 0·6 | 0·7 | 0·8 | 0·9 |
|---|---|---|---|---|---|---|---|---|---|
| $f_{H_2O}$ ..... | 4·28 | 3·00 | 2·25 | 1·85 | 1·60 | 1·48 | 1·39 | 1·32 | 1·21 |

## Experimental

p-*Methoxyphenyltrimethylsilane.*—Chlorotrimethylsilane (54 g.) was boiled under reflux for 7 hr. with the Grignard reagent from *p*-methoxyphenyl bromide (100 g.) and magnesium (14 g.) in ether (200 ml.). Hydrolysis, followed by fractionation of the ethereal layer, gave p-*methoxyphenyltrimethylsilane* (31 g.), b. p. 222·5—223·5°. The product was redistilled in nitrogen, and a middle sample (of *ca.* 2 g.), $n_D^{13\cdot5}$ 1·5073, was used (Found: C, 66·7; H, 9·1. $C_{10}H_{16}OSi$ requires C, 66·6; H, 8·9%).

*Cleavage of* p-*Methoxyphenyltrimethylsilane and Trimethylphenylsilane.*—Methanol (46 ml.) *p*-methoxyphenyltrimethylsilane (11·5 g.), and hydrochloric acid (5·4 ml.; s.g. 1·18; sufficient to make the mixture about 1N in acid) were boiled for 3½ hr. The mixture was poured into water; drying and fractionation of the ether extract gave hexamethyldisiloxane (4·0 g., 80%) and anisole (6·5 g., 93%).

Trimethylphenylsilane under the same conditions gave small amounts of hexamethyldisiloxane and benzene, and 93% of unchanged material.

*Ultra-violet Absorption Spectra.*—A Unicam S.P. 500 spectrophotometer was employed. In methanol (redistilled "AnalaR" material, probably slightly aqueous) the absorption curves of anisole and *p*-methoxyphenyltrimethylsilane are similar in shape but that of the latter is displaced by *ca.* 30 Å towards the visible and the extinction coefficients at both maxima are less. The maxima are: anisole; 2710 (ε, 1780), 2775 (ε, 1530), and 2647 Å (inflexion); *p*-methoxyphenyltrimethylsilane; 2735 (ε, 1380), 2805 (ε, 1260), and 2664 Å (inflexion). The curves cross at 2757 (ε, 2120) and 2733 Å (ε, 1370). The presence of dioxan (<10%) displaces the curves slightly. The wave-lengths chosen for spectrophotometric assay in the rate studies were 2700 Å [ε = 1720 (anisole) and 1160 (*p*-methoxyphenyltrimethylsilane)], 2820 Å (ε, 240 and 980, respectively), and either 2757 or 2755 Å depending upon whether the runs were in methanol or dioxan.

Trimethylsilanol, hexamethyldisiloxane, and methoxytrimethylsilane do not absorb in this spectral region.

*General.*—For kinetic measurements, "AnalaR" methanol was dried by Bjerrum and Zechmeister's method (*Ber.*, 1923, **56**, 894), and dioxan was purified by Eigenberger's method (*J. pr. Chem.*, 1931, **130**, 75) and dried by boiling it with sodium.

Volume changes on mixing have been neglected except in calculating the activity coefficients of water in dioxan: "20% water–methanol" refers to a solution consisting of 20 ml. of water made up to 100 ml. with methanol.

*Kinetic Measurements.*—All runs were carried out in a thermostat at 49·7° ± 0·02°.

For the runs in aqueous methanol, 1 ml. of aqueous acid of known strength was added to 10 ml. of an 0·02M solution of *p*-methoxyphenyltrimethylsilane in methanol or 20% water–methanol contained in the thermostat. At intervals, 1-ml. samples of the mixture were withdrawn and made up to 10 ml. with methanol, and the optical density, *D*, of the resulting solution was determined against the appropriate solvent blank at 2700, 2757, and 2820 Å, 0·5-cm. cells and a fixed slit width of 0·3 mm. being used. Since evaporation of the reaction mixture was serious during long periods, the values of $D_\infty$ were obtained with the appropriate solution of anisole. When an 0·2M-solution of the silane was used, with hundredfold dilution of the 1-ml. sample for assay, the rate constant was unaffected.

For runs in dioxan, 1 ml. of an 0·2M solution of the silane in dioxan was added to 10 ml. of aqueous dioxan of known acid concentration. The 1-ml. portions withdrawn were *added* to 10 ml. of methanol, and the optical density was determined as before, but at 2700, 2755, and 2820 Å. Values of $D_\infty$ were again determined by use of anisole, but in sample checks these agreed well with figures for the reaction mixture after a time equal to ten times the half-life.

For runs in methanol the optical density at 2757 Å was used only to indicate whether

evaporation was serious, and a run in which it changed by more than 5% was rejected. For runs in dioxan the optical density at 2755 Å was used to correct the $D$ (2820 Å) figures for errors in volume (particularly pipette-drainage errors) involved in rapid withdrawal of the 1-ml. samples. The $D$ (2700 Å) values could not be accurately determined at the concentrations employed and were used only to confirm that the reaction was following the expected course. Reactions were followed to more than 60% completion.

The rate constant is given by

$$k_t = 2{\cdot}303 \log [D_0(2820\text{ Å}) - D_\infty(2820\text{ Å})]/[D_t(2820\text{ Å}) - D_0(2820\text{ Å})]$$

Values of $k$ were obtained from the slope of the straight-line plot of log $[D_t(2820\text{ Å}) - D_\infty(2820\text{Å})]$ against time, but rate constants calculated throughout the reaction are included in the following typical runs. (The figures in parentheses for zero and infinity readings were determined by use of anisole solutions.)

(*a*) Solvent; 9 vol.-% water in methanol : [HCl] (added), 6·43N : temp., 49·7°.

| Time, min. | 0 | 9 | 17 | 28 | 38 | 52 | 76 | ∞ |
|---|---|---|---|---|---|---|---|---|
| $10^3D$(2757 Å) | — | 1117 | 1142 | 1122 | 1142 | 1150 | 1142 | — |
| $10^3D$(2700 Å) | (1100) | 1176 | 1257 | 1304 | 1372 | 1430 | 1486 | (1620) |
| $10^3D$(2782 Å) | 890 | 797 | 718 | 633 | 567 | 498 | 405 | ( 230) |
| $10^4k$, min.$^{-1}$ | — | 172 | 179 | 177 | 173 | 175 | 175 | — |

$k$ from graph, 175 × $10^{-4}$ min.$^{-1}$.

(*b*) Solvent : 45·5 vol.-% water in dioxan : [HCl], 0·794N : Temp., 49·7°.

| Time, min. | 0 | 16 | 31 | 48 | 65 | 92 | 120 | 200 | ∞ |
|---|---|---|---|---|---|---|---|---|---|
| $10^3D$(2755 Å) | (1055) | 1062 | 1062 | 1055 | 1043 | 1058 | 1052 | 1054 | — |
| $10^3D$(2700 Å) | (972) | 1038 | 1092 | 1129 | 1166 | 1240 | 1287 | 1375 | (1480) |
| $10^3D$(2820 Å) | — | 780 | 724 | 660 | 606 | 547 | 490 | 378 | — |
| $10^3D$(2820 Å) corr.* | (847) | 775 | 719 | 662 | 613 | 546 | 491 | 378 | ( 247) |
| $10^4k$, min.$^{-1}$ | — | 792 | 772 | 768 | 762 | 756 | 750 | 751 | — |

$k$ from graph, 764 × $10^{-4}$ min.$^{-1}$. * $D$(2820 Å) corr. = $D$(2820 Å) × 1·055/$D$(2755 Å).

*Determination of Acidity Functions.*—Braude's method (*loc. cit.*) was employed, *p*-nitroaniline being used as indicator (B). The solutions were made up as for the reaction media, so that for the methanolic solutions 1 ml. of aqueous acid of strength $c_A$ was added to 10 ml. of anhydrous methanol or 20% water–methanol containing the indicator (4 × $10^{-4}$M) or nitrobenzene (0·025M). For measurements in aqueous dioxan, 1 ml. of a solution of the indicator (1·4 × $10^{-3}$M) or of nitrobenzene (0·33M) in dioxan was added to 10 ml. of aqueous dioxan ($11x$/10 ml. of water in 100 ml. of solution) containing hydrochloric acid of concn. $11c_A'$/10M. Because volume-additivity is assumed, and because pipettes were not calibrated for all the solutions, the values of the indicator ratio, $I = [BH^+]/[B]$, are more accurate than the absolute values of the extinction coefficients. Measurements were at *ca.* 18°. In the following tables

(*a*) Solvent, 9% water-methanol. Acid, hydrochloric. $\lambda_N = \lambda_A = 374$ mμ. $\varepsilon_N$, 15,950. $\varepsilon_B$, 60.

| $c_A$, N | 11·40 | 7·63 | 6·43 | 5·74 | 4·27 | 3·38 | 2·306 | 1·451 | 1·079 |
|---|---|---|---|---|---|---|---|---|---|
| $\varepsilon_A$ | 2,820 | 5,460 | 6,740 | 7,400 | 9,440 | 10,670 | 12,330 | 13,850 | 14,370 |
| $I$ | 4·75 | 1·94 | 1·38 | 1·16 | 0·693 | 0·497 | 0·295 | 0·152 | 0·111 |
| $-H$ | 0·277 | 0·666 | 0·815 | 0·888 | 1·113 | 1·257 | 1·484 | 1·771 | 1·911 |

(*b*) Solvent, 27% water–methanol. Acid, hydrochloric. $\lambda_N = \lambda_A = 380$ mμ. $\varepsilon_N$, 15,770. $\varepsilon_B$, 40.

| $c_A$, N | 7·630 | 6·43 | 5·74 | 4·27 | 3·38 |
|---|---|---|---|---|---|
| $\varepsilon_A$ | 8,260 * | 9,270 | 9,830 | 11,260 | 12,320 |
| $I$ | 0·914 | 0·705 | 0·607 | 0·402 | 0·281 |
| $-H$ | 0·993 | 1·106 | 1·171 | 1·350 | 1·505 |

* $\lambda_A = 381$ mμ.

(*c*) Solvent, 9% water–methanol. Acid, perchloric. $\lambda_N = \lambda_A = 374$ mμ. $\varepsilon_N$, 15,950. $\varepsilon_B$, 60.

| $c_A$, N | 5·74 | 4·12 | 2·17 | 0·918 |
|---|---|---|---|---|
| $\varepsilon_A$ | 6,420 | 8,840 | 12,340 | 14,550 |
| $I$ | 1·50 | 0·809 | 0·294 | 0·097 |
| $-H$ | 0·779 | 1·046 | 1·486 | 1·968 |

(*d*) Solvent, $x$% water–dioxan. Acid, hydrochloric.

| $x$ | $c'_A$, N | $\lambda_N$, mμ | $\varepsilon_N$ | $\varepsilon_A$ | $\lambda_A$, mμ | $\varepsilon_S$ | $I$ | $-H$ |
|---|---|---|---|---|---|---|---|---|
| 14·5 | 0·278 | 369 | 16,790 | 13,280 | 369 | 90 | 0·266 | 1·43 |
| 14·5 | 0·421 | 369 | 16,790 | 10,670 | 367 | 90 | 0·573 | 1·20 |
| 18·2 | 0·526 | 370 | 16,790 | 10,780 | 370 | 80 | 0·561 | 1·20 |
| 23·2 | 0·666 | 371 | 16,740 | 9,870 | 372 | 80 | 0·674 | 1·13 |
| 27·3 | 0·789 | 374 | 16,650 | 9,860 | 374 | 70 | 0·693 | 1·11 |
| 36·0 | 1·045 | 377 | 16,621 | 8,440 | 376 | 60 | 0·976 | 0·96 |
| 45·5 | 1·055 | 380 | 16,280 | 7,330 | 380 | 50 | 1·230 | 0·86 |
| 45·5 | 0·794 | 381 | 16,500 | 10,010 | 381 | 50 | 0·652 | 1·14 |
| 45·5 | 1·324 | 381 | 16,280 | 5,310 | 381 | 50 | 2·08 | 0·64 |
| 45·5 | 0·526 | 380 | 16,500 | 12,650 | 378 | 60 | 0·306 | 1·47 |
| 47·3 | 0·870 | 380 | 16,500 | 8,680 | 381 | 50 | 0·906 | 1·00 |
| 51·8 | 0·973 | 381 | 16,310 | 7,260 | 382 | 40 | 1·26 | 0·86 |

$\lambda_N$ and $\varepsilon_N$ refer to the wave-length and molecular-extinction coefficients of the indicator at the absorption peaks in neutral solution, $\lambda_A$ and $\varepsilon_A$ are the corresponding values in acid solution, and $\varepsilon_S$ refers to that of the nitrobenzene solution at $\lambda_A$. The acidity function is given by $H = \log I - 0{\cdot}954$, where $I = (\varepsilon_N - \varepsilon_A)/(\varepsilon_A - \varepsilon_S)$.

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UNIVERSITY COLLEGE, LEICESTER. [*Received, April 25th,* 1953.]

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## 628. *The Reversibility of the Adsorption of Catalyst Poisons. Part II.* Derivatives of Arsenic.*

By E. B. MAXTED and G. T. BALL.

Platinum hydrogenation catalysts poisoned at room temperature by a stable arsenic derivative such as dimethylphenylarsine can be revived easily and completely by desorbing the poison by the competitive adsorption of an unsaturated compound (*cyclo*hexene). At higher temperatures, complications arise owing to the decomposition of the poison on the platinum surface; and the degree of revival is incomplete. Poisons such as arsenious oxide or potassium antimonyl tartrate, which readily pass into arsine or stibine under hydrogenating conditions, resist desorptive revival even at room temperature, since the arsine or stibine readily decomposes into a non-desorbable form.

THE revival of hydrogenation catalysts which have been poisoned by arsenic or antimony compounds is of interest since this type of poison cannot be rendered permanently innocuous by chemical detoxication, in that the shielded and therefore non-toxic derivatives formed by the usual detoxication treatment are converted, under hydrogenating conditions, into toxic arsine or stibine.

In the present paper, the effectiveness of the alternative revivification method (Part I *) involving a desorption, and especially a desorptive displacement of the adsorbed poison from the catalyst surface by the competitive adsorption of an unsaturated substance, has been examined for catalysts poisoned by derivatives of arsenic. If the poisoning of the catalyst has been carried out at room temperature with a relatively stable arsenic derivative, such as a substituted arsine (dimethylphenylarsine), it has been found that this desorptive method leads to an easy revival to a state in which the catalyst completely regains its unpoisoned activity. The degree of the possible revival is, however, diminished if the catalyst containing the adsorbed poison is heated to 100°, this effect being probably due to the decomposition of part of the poison into a non-desorbable form. This decomposition effect occurs even at room temperature if the catalyst has been poisoned by arsenic or antimony compounds which are known readily to form arsine or stibine under hydrogenating conditions. The probability that the failure to revive such catalysts by desorption is due to decomposition, rather than to an initially irreversible adsorption, is

* Part I, *J.*, 1952, 4284.

strengthened by previous and somewhat parallel work with hydrogen sulphide. In this much earlier work (Maxted, *J.*, 1919, **115**, 1050) it was found that, if hydrogen sulphide is adsorbed on palladium and the adsorption complex evacuated at 100°, hydrogen in place of hydrogen sulphide is pumped off and the sulphur is retained as a sulphide by the metal; and it seems probable that arsine or stibine would decompose even more easily, especially by reason of the weakness of the arsenic–hydrogen or antimony–hydrogen bonds (heats of formation of $H_2S = +5{\cdot}3$; $AsH_3 = -43{\cdot}5$; $SbH_3 = -34{\cdot}8$ kcal.).

## Experimental

The stock of catalyst, from which 0·025-g. portions were weighed out as required, was made from chloroplatinic acid by alkaline formate reduction, the precipitated platinum being washed exhaustively in a shaker, with separation of the black by centrifuging between the individual washes, before being dried at 100°. The poisons were applied in acetic acid solution, and the revival of the poisoned catalyst, as a result of successive displacements of the adsorbed poison by *cyclo*hexene, was followed by means of hydrogenation runs.

*Revival of Catalysts poisoned by Dimethylphenylarsine.*—This poison was taken as a convenient arsenic derivative which is not too easily decomposed by platinum in the presence of hydrogen. In a series of revivification tests, results of which are summarised in Fig. 1, 0·025 g. of platinum catalyst was poisoned by treatment in a closed pipette at room temperature with $2 \times 10^{-4}$ mole of dimethylphenylarsine in 9 c.c. of acetic acid, the system being allowed to remain for 16 hr., with occasional shaking in order to allow the adsorption of the poison to proceed. In order to measure the activity of the poisoned catalyst by means of a hydrogenation run, 1 c.c. of *cyclo*hexene (which is necessary to complete the hydrogenation system but unavoidably causes some of the poison to move from the catalyst surface into the free phase) was next added. Hydrogen was then admitted to the pipette, and the system was shaken in a hydrogenation shaker under standardised conditions at 30°. This hydrogenation test with the poisoned catalyst is shown in Curve II. Curves III, IV, and V show the progressive displacement of the poison, indicated by the gradual recovery in the activity of the platinum, as the result of washing the poisoned catalyst prior to the new hydrogenation test, respectively with one, two, and three fresh charges of *cyclo*hexene, each wash being carried out by separating the platinum from the supernatant liquid in a centrifuge, decanting this liquid, and shaking the platinum at room temperature in the absence of hydrogen with a fresh displacement charge consisting of 1 c.c. of *cyclo*hexene and 9 c.c. of acetic acid. It will be seen that a complete recovery of the original activity, shown in Curve I which represents a blank hydrogenation run carried out with a charge from which the poison had been omitted, was obtained after three washes with the unsaturated substance: indeed, this limit was very nearly approached even after two washes.

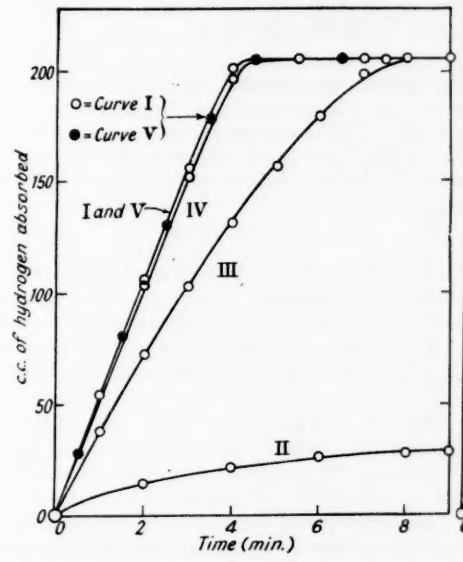
As a slight variation in the above procedure, the initial hydrogenation run with a poisoned catalyst was, in a further series, carried out with platinum which had been poisoned by allowing $2 \times 10^{-4}$ mole of the poison, in the standard hydrogenation charge, to remain in contact with the platinum for 30 min. only, with continuous shaking, instead of for 16 hr. as before. In this case, the degree of poisoning obtained was less than for the longer time of contact; *e.g.*, the hydrogenation run with the poisoned catalyst gave an absorption of 33·4 c.c. of hydrogen after 3 minutes' hydrogenation, compared with 18·9 c.c. for the longer poisoning time under otherwise identical conditions; but the revival, on washing of the poisoned catalyst with successive charges containing *cyclo*hexene, took place normally. Thus, after two washes of the poisoned platinum with *cyclo*hexene, the activity was restored to a value equal to that given in a blank run with fresh unpoisoned catalyst.

*Revival of Catalysts poisoned at a Higher Temperature.*—In this series, the initial poisoning of the catalysts, prior to the revivification treatment, was carried out at 100° instead of at room temperature. In the set of hydrogenation curves contained in Fig. 2, Curve II shows the activity of 0·025 g. of catalyst poisoned by being previously shaken for 2 hr. at 100° in a closed pipette with $2 \times 10^{-4}$ mole of dimethylphenylarsine in 9 c.c. of acetic acid. The subsequent revivification procedure—the results of which are given in Curves III, IV, and V—was similar to that used for the corresponding series of Fig. 1. With the catalyst poisoned at this higher temperature, the original activity, as shown in the blank run (Curve I), was not reached as a result of the revivification treatment, in that the exposure of the poison to a temperature of 100°, in contact with the platinum, apparently induces a partial change into a form in which it can no longer be removed by desorptive displacement with *cyclo*hexene. The limit of its

removal seems to be reached after two successive treatments with the unsaturated substance, since Curve IV (two washes with *cyclo*hexene) is identical with Curve V (three washes).

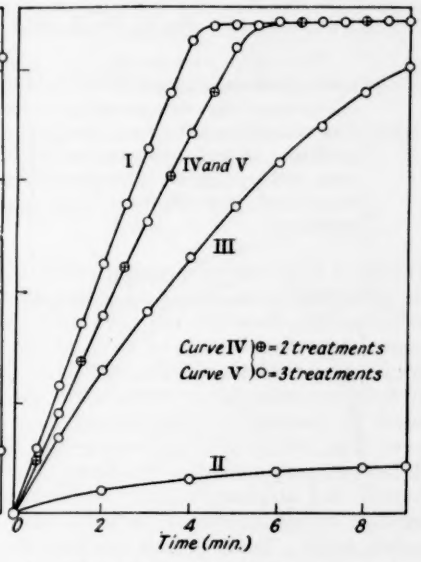
This existence of a limit to the desorptive revival of catalysts poisoned at higher temperatures was confirmed by two other series of tests. In the first of these, the poisoning time at 100° was reduced from 2 hr. to 30 min., under which conditions slightly less poison was adsorbed, and the activity of the poisoned platinum was accordingly a little greater than in Curve II of Fig. 2; but the limit of the revival by subsequent repeated washing with *cyclo*hexene did not differ appreciably from that in the preceding series. Very similar results were obtained by reducing the adsorption of poison in the initial poisoning operation by adding the dimethylphenylarsine to a complete hydrogenation change (namely, in the presence of the 1 c.c. of *cyclo*hexene required as an unsaturated substance, in place of in the presence of acetic acid alone, during a 2 hr.'

FIG. 1. *Desorptive displacement of* $AsMe_2Ph$ *from* Pt. *Poisoning temp.* = 20°.




I (blank) and V. (3 Treatments.)
II. Poisoned catalyst before treatment.
III. Poisoned catalyst after one treatment with *cyclo*hexene.
IV. (2 Treatments.)

FIG. 2. *Desorptive displacement of* $AsMe_2Ph$ *from* Pt. *Poisoning temp.* = 100°.




I. Blank (no poison added).
II. Poisoned catalyst before treatment.
III. Poisoned catalyst after one treatment.

poisoning time at 100°). The subsequent revival by washing with successive charges containing *cyclo*hexene did not greatly pass beyond the limiting value shown in Fig. 2.

*Attempted Desorptive Revival of Platinum poisoned with Arsine or Stibine.*—It is known that arsenious oxide, on treatment with nascent hydrogen, or with hydrogen in the presence of platinum, readily passes into arsine. In the present work, 0·025 g. of the stock platinum catalyst was first poisoned by being shaken for a few minutes in hydrogen at room temperature with a known amount of arsenious oxide dissolved in 9 c.c. of acetic acid, following which 1 c.c. of *cyclo*hexene was added and the system subjected to the usual hydrogenation run at 30°. It was found that the platinum was extremely sensitive to arsenic in this form and that the use of $10^{-5}$ g.-atom of arsenic ($5 \times 10^{-6}$ mole of $As_2O_3$) was sufficient to reduce the activity from an unpoisoned value corresponding with the absorption of about 60 c.c. of hydrogen per min. in a blank run with unpoisoned catalyst, down to an absorption of about 2 c.c. per min. in the poisoned run. The poisoned catalyst was then subjected to the usual revivification treatment; but, after three successive treatments with 1 c.c. of *cyclo*hexene in 9 c.c. of acetic acid, the activity did not rise appreciably above its poisoned value.

In corresponding tests with an antimony compound which is easily converted into stibine,

similar results were obtained. Thus, on poisoning of 0·025 g. of platinum, in hydrogen at room temperature, with $10^{-5}$ mole of potassium antimonyl tartrate, the activity of the poisoned catalyst corresponded with an absorption rate of about 2·5 c.c. of hydrogen per min. in the hydrogenation test, and with a rate of about 4 c.c. after three washings with *cyclo*hexene, again compared with a blank rate of the order of 60 c.c. per min.

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THE UNIVERSITY, BRISTOL. [*Received, May 5th,* 1953.]

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## 629. *Synthesis of* cis- *and* trans-*Octadecenes. Selective Catalytic Hydrogenation of Acetylenes.*

By B. B. ELSNER and P. F. M. PAUL.

The eight *cis-n*-octadecenes have been prepared by selective catalytic hydrogenation and six of the eight possible *trans-n*-octadecenes by partial reduction of the corresponding octadecynes with sodium and liquid ammonia. The suitability of various catalysts for the selective hydrogenation has been studied. Starch-supported colloidal palladium, poisoned palladium, Raney iron, and pyrophoric Raney nickel were unsuitable: non-pyrophoric Raney nickel and, particularly, a nickel–copper catalyst were, however, sufficiently selective.

OLEFINS of high molecular weight produced by cracking of high-boiling fractions of petroleum constitute new sources of long-chain acids and alcohols. A series of the isomeric *n*-octadecenes, therefore, has been synthesised in a high degree of purity and free from isomers for determination of their physical constants. The usual methods such as dehydration of alcohols, dehalogenation of dihalides, removal of the elements of hydrogen halide from monohalides, thermal cleavage of esters, etc., could not be employed since they cannot be considered unambiguous. For example, Asinger (*Ber.*, 1942, **75**, 1260) has shown that freshly prepared magnesium bromide can cause considerable isomerisation of alk-1-enes; preparation of the latter, therefore, by the Grignard reaction between allyl bromide and alkylmagnesium bromides can no longer be considered unambiguous. In any case such methods are excluded when the synthesis of pure *cis*- and *trans*-olefins is contemplated. In the present work the *cis-n*-octadecenes have been prepared by selective catalytic hydrogenation, and the *trans*-octadecenes by partial reduction of the corresponding octadecynes with sodium and liquid ammonia.

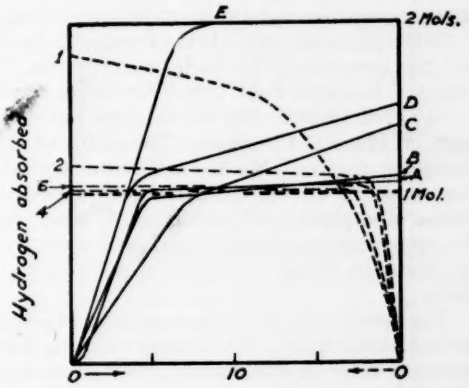
Early workers in this field claimed that the catalytic hydrogenation of acetylenes could be directed to give either the *cis*- or the *trans*-olefins by varying the rate of hydrogenation, the catalyst, or the temperature. Despite contradictory claims it finally became established that catalytic hydrogenation of disubstituted acetylenic hydrocarbons led exclusively to *cis*-olefins; and, further, that addition of the second molecule of hydrogen to an olefin derived from a disubstituted acetylene was much slower, whereas with monosubstituted acetylenes the rates for the first and the second molecule were little different.

In the present work, no evidence of contamination of *cis*- with *trans*-isomers has been found.

*Selective Catalytic Hydrogenation of Acetylenes.*—The selectivity of the following catalysts was studied. Starch-supported colloidal palladium, prepared according to Bourguel [*Bull. Soc. chim.*, 1927, (4E), **41**, 1444], exhibited only slight specificity with oct-1-yne and octadec-9-yne. In addition, the rate of hydrogenation was very slow. Raney iron, prepared by Paul and Hilly's method [*ibid.*, 1939, (5E), **6**, 218], did not promote hydrogenation of octadec-9-yne at room temperature. This catalyst, although generally considered incapable of promoting the hydrogenation of olefins, caused formation of the alkane when used with *n*-octadec-9-yne at 110°/50 atm. Freshly prepared Raney nickel (cf. Mozingo, *Org. Synth.*, 1941, **21**, 15) gave much higher rates of hydrogenation at atmospheric pressure

than did palladium on starch. It was not selective with monoalkylacetylenes. In the case of the dialkylacetylenes, however, the rate of absorption decreased progressively. Campbell and O'Connor (*J. Amer. Chem. Soc.*, 1941, **63**, 216) prepared several *cis*-olefins by partial hydrogenation at 5 atm. in presence of this catalyst. Recent work has shown that a reactive catalyst can be made more selective by poisoning. A quinoline-poisoned palladium–charcoal catalyst has been successfully used by Isler *et al.* (*Helv. Chim. Acta*, 1947, **30**, 1911) and Heilbron, Jones, Toogood, and Weedon (*J.*, 1949, 2028); Ruzicka and Miller (*Helv. Chim. Acta*, 1939, **22**, 755) favoured the use of palladium–calcium carbonate in pyridine suspension; but both of these are insufficiently active for hydrogenation of octadecynes. When, however, palladium–calcium carbonate was used in suspension in ethyl acetate–methanol (2 : 1), containing 0·25% of pyridine, selective hydrogenation did take place although the absorption rate was slow (K. J. Parker, personal communication). The selective palladium catalyst described by Lindlar (*Helv. Chim. Acta*, 1952, **35**, 446) and the piperidine–zinc acetate-poisoned nickel catalyst employed by Oroshnik, Karmas, and Mebane (*J. Amer. Chem. Soc.*, 1952, **74**, 295) were not known to us at the time of the investigation.

Aged Raney nickel was much more selective than freshly prepared Raney nickel. The




Full lines: Non-pyrophoric Raney nickel.
Broken lines: Nickel–copper.

*A*, *Octadec*-9-*yne*.
*B*, *Octadec*-3-*yne*.
*C* and 6, *Octadec*-6-*yne*.
*D* and 2, *Octadec*-2-*yne*.
*E* and 1, *Octadec*-1-*yne*.
4, *Octadec*-4-*yne*.

marked selectivity of Raney nickel which had been stored under ethanol for six months is demonstrated by the two mean rates of hydrogenation for each of the octadecynes which are listed in Table 1 (p. 3159).

*Nickel–Copper Catalyst.*—Aged Raney nickel has an obvious disadvantage. A readily available and very selective catalyst was produced by treatment of pyrophoric Raney nickel with ethanolic copper acetate, so that up to 10% of copper was deposited on the nickel. Two factors influence the specificity of this catalyst; first, the activity of Raney nickel which itself depends on the method of preparation and the time of storage; and, secondly, the copper–nickel ratio: the less active the Raney nickel, the less copper is needed and *vice versa*. The selectivity can be varied on this basis to suit the particular acetylenic compound. Hydrogenation of small amounts (0·2—0·5 g.) of the octadecynes to olefins by use of this catalyst at atmospheric pressure and room temperature can be effected in a few minutes, though, of course, it depends also on the amount of catalyst, the effectiveness of stirring, and the age of the catalyst. The selectivities of this catalyst and aged Raney nickel are compared in the Figure.

Non-pyrophoric Raney nickel and the nickel–copper catalyst were used for preparation of the *cis*-octadecenes.

trans-*Octadecenes.*—No satisfactory method for the partial reduction of acetylenes to *trans*-olefins was available until Campbell and Eby (*ibid.*, 1941, **63**, 216) showed that acetylenes were reduced exclusively to, and only so far as, *trans*-olefins by sodium in liquid ammonia. However, our acetylenes resisted such reduction at −35°; use of ether as a solvent (cf. Henne and Greenlee, *ibid.*, 1943, **65**, 216, 2683) also proved ineffective. A

modification of Henne and Greenlee's method whereby the reaction was carried out under pressure at room temperature in a tilting autoclave was successful, reaction being complete in 10—12 hours and yields almost quantitative.

Both *cis*- and *trans*-olefin were purified by low-temperature crystallisation from acetone (for method and apparatus see Smith, *J.*, 1939, 944, and Elsner and Paul, *J.*, 1951, 893), in which they were markedly less soluble than the parent acetylenes. This purification, followed by fractional distillation, was repeated until the freezing points were constant; the final physical properties are recorded in Table 2 (p. 3160).

Of the octadecene series, only the *cis*- and the *trans*-9-isomer have been prepared previously, namely, by Boeseken and Belinfante (*Rec. Trav. chim.*, 1926, **45**, 914) from oleic and elaidic acid. Their values for the physical constants are not in agreement with ours.

*Physical Constants.*—*trans*-Octadecenes have higher freezing points than the *cis*-isomers, in agreement with the data for homologues (Campbell and Eby, *loc. cit.*). Further, the difference in freezing point between the corresponding *cis*- and *trans*-isomers increases as the double bond is moved towards the centre of the chain.

Except in the case of the octadec-2-enes, the *trans*-forms have the lower densities, also in agreement with recorded data for the lower homologues.

The refractive indices of *cis*- and *trans*-octadec-2- and -3-ene are the same, whereas in all other cases the *cis*-form has the higher value.

Of the physical constants the freezing points show the greatest differences, in agreement with the general rule for such cases (Brooks, " Chemistry of the Non-Benzenoid Hydrocarbons," Reinhold Publ. Corp., New York., 2nd Edn., 1950, p. 240).

*Infra-red Spectra.*—We are indebted to Dr. E. C. Leisegang (at that time of the Department of Physical Chemistry, University of Oxford) for determination of the infra-red absorption spectra. Marked differences appear between the spectra of the *cis*- and the *trans*-forms in all the cases studied. *trans*-Forms are readily recognised by the very intense absorption band at 970 $cm.^{-1}$, where the *cis*-isomers have only weak bands. All the compounds have intense bands at 720 $cm.^{-1}$; the contours of the bands of the *cis*-forms are, however, broad and rounded, whereas the bands of the *trans*-forms occur as sharp peaks.

The appearance of the spectra support Sheppard and Simpson's interpretation (*Quart. Reviews*, 1952, **6**, 1). The intense band at 970 $cm.^{-1}$ in this series of *trans*-disubstituted ethylenes may be due to the out-of-plane-bending vibration of the ethylene grouping, while the broadening of the bands in the *cis*-compounds at 720 $cm.^{-1}$ may be due to the overlap of the out-of-plane-bending mode of the *cis*-form with the rocking-frequency usually found at about this frequency.

## Experimental

F. p. and m. p. measurements were made with Anschütz-type thermometers. Analyses were by Mr. F. C. Hall, Dyson Perrins Laboratory.

*Hydrogenation Apparatus.*—Hydrogenations were carried out under 20 mm. excess pressure. Standard ground-glass joints were used where possible, and glass-to-glass connections were made with " Polythene " tubing. Steady agitation was achieved by means of a magnetic stirrer and was controlled so that the vortex in the liquid just reached the bottom of the flask and no splashing occurred. The reservoir was calibrated by hydrogenation of cinnamic acid.

*Selectivity of Catalysts.*—(a) *Starch-supported colloidal palladium.* Hydrogenation in ethyl acetate (25 c.c.) solution of oct-1-yne (0·696 g.) and octadec-9-yne (1·685 g.), each in the presence of 25 c.c. of catalyst solution (Bourguel, *loc. cit.*), was complete in 140 min.; 302 and 320 c.c. respectively at 23°/763 mm. were absorbed.

A gradual decrease in the rate of hydrogenation after the absorption of the first mol. occurred only in the case of octadec-9-yne.

(b) *Raney nickel.* The catalyst was transferred, when required, to a burette fitted with a 4-mm. cone tap and after settlement, a measured volume was discharged into the hydrogenation flask. Pure oct-1-yne (0·661 g.), octadec-3-yne (0·496 g.), and octadec-9-yne (1·246 g.), in ethyl acetate (25 c.c.), were hydrogenated in the presence of Raney nickel (0·5 c.c.). With oct-1-yne no break occurred in the rate of hydrogenation; with the two octadecynes marked changes in the rate occurred but only after approx. 1·5 mols. had been absorbed.

(c) *Raney iron.* This catalyst did not promote hydrogenation of octadec-9-yne at atmospheric pressure. Hydrogenation in an autoclave (at 110°/50 atm.) for 6 hr. gave octadecane, m. p. 27·5—28° (Found : C, 85·2; H, 14·76. Calc. for $C_{18}H_{38}$ : C, 85·0; H, 15·0%).

*Quinoline-poisoned Palladium–Charcoal.*—Octadec-2-yne (0·301 g.) was hydrogenated in ethyl acetate (10 c.c.) in the presence of 8% palladium–charcoal (0·02 g.) and quinoline (0·02 g.). No hydrogen was absorbed in 20 min. When more palladium–charcoal (0·03 g.) was added reduction started after 15 min.; after 2 hours one mol. had been absorbed.

*Pyridine-poisoned Palladium–Calcium Carbonate.*—Octadec-6-yne (0·395 g.), in ethyl acetate (15 c.c.), methanol (8 c.c.), and pyridine (0·05 g.), was hydrogenated with 5% palladium–calcium carbonate (0·1 g.). One mol. of hydrogen (38 c.c.) was absorbed in 18 min. A further 4 c.c. of hydrogen were absorbed during the next 30 min.

*Non-pyrophoric Raney Nickel.*—Aged Raney nickel which was no longer pyrophoric when exposed to air was sufficiently active to promote hydrogenation of alkylacetylenes. The rate of addition of the first mol. was still very rapid but with the dialkylacetylenes the second mol. was added at a much reduced rate (cf. Figure and Table 1). With octadec-1-yne there was little difference in the rates of addition of both the first and the second mol. of hydrogen. Hydrogenation curves for octadec-4-, -6-, -7-, and -8-yne have been excluded from the Figure for clarity.

TABLE 1.

| Octadec-*x*-yne, *x* | Wt. (g.) | Theor. $H_2$ absorption (c.c./temp./mm.) | Change in rate at (c.c.) | Rates of hydrogenation (c.c./min.) Initial | Secondary |
|---|---|---|---|---|---|
| 1 | 0·326 | 64·1/21°/747 | — | 9·15 | 7·1 |
| 2 | 0·378 | 74·4/21°/746 | 40 | 10·0 | 1·5 |
| 3 | 0·412 | 81·4/21°/744 | 39·5 | 7·9 | 0·5 |
| 4 | 0·423 | 83·8/20°/738 | 39·0 | 6·5 | 0·2 |
| 5 | 0·413 | 80·3/17°/745 | 40·0 | 6·0 | 0·25 |
| 6 | 0·416 | 80·2/20°/759 | 40·0 | 5·0 | 0·5 |
| 7 | 0·392 | 75·9/19°/754 | 38·0 | 6·5 | 0·2 |
| 8 | 0·401 | 76·9/20°/763 | 39·0 | 7·0 | 0·4 |
| 9 | 0·354 | 68·5/20°/756 | 35·0 | 7·0 | 0·5 |

*Preparation of the Nickel–Copper Catalyst.*—Ethanol-moist pyrophoric Raney nickel (18 g.) was stirred in a solution of copper acetate (2 g.) in ethanol (120 c.c.) on the water-bath for 20 min. The catalyst was washed by decantation with ethanol (3 × 60—80 c.c.), then with ethyl acetate (3 × 60—80 c.c.). The catalyst was kept under ethyl acetate.

In the hydrogenation of octadec-4-yne, for example, the catalyst (0·5 c.c.), suspended in ethyl acetate (20 c.c.), was stirred under hydrogen until saturated, before the acetylene (0·286 g.) was added. The theoretical volume of hydrogen (28 c.c.) was absorbed in 3 min. and no further absorption occurred during the next 10 min. The other dialkylacetylenes behaved similarly. In the case of octadec-1-yne (0·323 g.) the first mol. (32 c.c.) was absorbed in 4 min. but the reduction did not then cease : the second mol. was absorbed, however, in 40 min. (cf. Figure).

The same catalyst could be used for the hydrogenation of a fresh specimen of the same acetylene or of another isomer with similar results, thus demonstrating that the activity of the catalyst was not impaired.

*Selectivity of Nickel–Copper Catalyst.*—The catalyst prepared from Raney nickel W.7 (Billica and Adkins, *Org. Synth.*, **29**, 24) made 2 weeks previously was inactive towards octadec-4-yne. This acetylene (0·26 g. each time) was used to test three nickel–copper catalysts prepared from highly pyrophoric Raney nickel (6 g. of ethanol-moist) made 2 days previously (cf. Mozingo, *loc. cit.*) and treated as above, but as follows : (*a*) Copper acetate (0·7 g.). One mol. of hydrogen was absorbed in 3 min.; reduction went on slowly until the second mol. was absorbed. (*b*) Copper acetate (1·0 g.). After 1 mol. had been absorbed in 5 min. the reduction stopped for about 3 min., then went on until the second equiv. was absorbed in 25 min. This catalyst was used 4 days later : absorption of the first mol. required 8 min., and reduction stopped for 6 min., then went on until the second equiv. was absorbed in 68 min. (*c*) Copper acetate (1·4 g.). The first mol. was absorbed in 5 min. and the reaction stopped during the next 6 min. Hydrogenation with this catalyst 7 days later reached the half-way stage in 8 min. and no further absorption of hydrogen occurred in the following 10 min.

cis-*Octadecenes.*—Non-pyrophoric Raney nickel or nickel–copper catalyst was employed in the preparation of the *cis*-olefins. Hydrogenation was interrupted when 1 mol. of hydrogen was absorbed. The crude olefins were purified immediately and their physical constants determined. Approx. 8 g. of the parent hydrocarbon were hydrogenated in each case. With

octadec-9-yne, for example, the acetylene (7·833 g.), in ethyl acetate (25 c.c.), was stirred under hydrogen in the presence of non-pyrophoric Raney nickel (0·5 c.c.). The rate of hydrogen absorption was constant (7 c.c./min.), and, when the theoretical volume had been absorbed (1 mol., 761 c.c. at 20°/752 mm.), stirring was discontinued and the catalyst removed immediately filtered off. The solvent was removed under reduced pressure and the product distilled immediately (b. p. 164°/9 mm.). A solution of the crude olefin in acetone (180 c.c.) was allowed to crystallise at −50° in the low-temperature filtration apparatus (cf. *J.*, 1951, 893). The f. p. (−30·4°) of the purified olefin was unaltered on further low-temperature recrystallisation. *cis*-Octadec-9-yne (5·5 g., 70%) was obtained as a colourless, odourless oil (b. p. 162°/8·5 mm., $n_D^{20}$ 1·4470, and $d_4^{20}$ 0·7916) (Found: C, 85·8; H, 14·4. Calc. for $C_{18}H_{36}$: C, 85·7; H, 14·3%). Boeseken and Belinfante (*loc. cit.*) record b. p. 190°/15 mm., m. p. < −15°, $n_D^{20}$ 1·4483, $d_4^{20}$ 0·7968.

trans-*Octadecenes.*—Prolonged treatment of the octadecynes with sodium and liquid ammonia by the methods of Campbell and Eby and of Henne and Greenlee (*locc. cit.*) failed. When the reductions were carried out in an autoclave at room temperature, however, the reactions proceeded to completion and the olefins were obtained in good yield. *E.g.*, octadec-9-yne (8·0 g.) in anhydrous ether (150 c.c.) was added to a pre-cooled stainless-steel tilting autoclave (1 l.). A solution of sodium (2·0 g.) in liquid ammonia (200 c.c.) was added quickly and the autoclave sealed and was shaken for about 14 hr. The liquid ammonia was then allowed to evaporate through the needle-valve. Ice (100 g.) was added and the product extracted with ether. The olefin (7·6 g.; b. p. 178—180°/18 mm.) was crystallised twice from acetone (175 c.c.) at −35° before being fractionally distilled. *trans*-Octadec-9-ene (6·6 g., 82%) was obtained as a colourless, odourless oil, b. p. 180°/18 mm., $n_D^{20}$ 1·4460, $d_4^{20}$ 0·7852, f. p. 4·8° (Found: C, 85·5; H, 14·3%). Boeseken and Belinfante (*loc. cit.*) report m. p. 2·0°, $n_D^{19}$ 1·4478, $d_4^{19}$ 0·7917.

TABLE 2.

| Octadecenes | B. p. (°/mm.) | F. p. | M. p. | $n_D^{20}$ | $n_D^{25}$ | $d_4^{20}$ | $d_4^{25}$ |
|---|---|---|---|---|---|---|---|
| *cis*-2- ..... | 173·5°/13 | 7·7° | 7·6° | 1·4470 | 1·4451 | 0·7922 | 0·7890 |
| *trans*-2- ..... | 174·0/15 | 13·5 | 13·2 | 1·4470 | 1·4450 | 0·7938 | 0·7902 |
| *cis*-3- ..... | 171·5/13 | 4·2 | 4·3 | 1·4447 | 1·4427 | 0·7902 | 0·7870 |
| *trans*-3- ..... | 177·0/16 | 10·3 | 10·2 | 1·4447 | 1·4427 | 0·7876 | 0·7847 |
| *cis*-4- ..... | 171·5/13 | −15·8 | −16·0 | 1·4468 | 1·4449 | 0·7910 | 0·7876 |
| *trans*-4- ..... | 183·5/22 | − 0·6 | − 0·7 | 1·4460 | 1·4441 | 0·7880 | 0·7851 |
| *cis*-5- ..... | 177·0/17 | −25·2 | −25·5 | 1·4460 | 1·4439 | 0·7898 | 0·7868 |
| *cis*-6- ..... | 181·0/19 | −19·2 | −19·0 | 1·4468 | 1·4450 | 0·7905 | 0·7874 |
| *trans*-6- ..... | 178·5/19 | 0·7 | 0·6 | 1·4461 | 1·4440 | 0·7894 | 0·7857 |
| *cis*-7- ..... | 186·0/23 | −33·5 | −33·2 | 1·4469 | 1·4450 | 0·7911 | 0·7880 |
| *trans*-7- ..... | 183·0/21 | − 3·8 | − 3·6 | 1·4460 | 1·4440 | 0·7877 | 0·7849 |
| *cis*-8- ..... | 182·5/21 | −19·5 | −19·5 | 1·4465 | 1·4448 | 0·7924 | 0·7993 |
| *cis*-9- ..... | 162·0/9 | −30·4 | −30·5 | 1·4470 | 1·4450 | 0·7916 | 0·7884 |
| *trans*-9- ..... | 180·0/18 | 4·8 | 5·0 | 1·4461 | 1·4440 | 0·7883 | 0·7852 |

*Infra-red Spectra of the Octadecenes.*—The spectra were obtained by means of a single-beam infra-red spectrometer with a rock-salt prism. A 0·2-mm. rock-salt liquid cell was used. The specimen of octadec-1-ene was warmed to 20—25°.

The spectra of the 2-, 4-, and 6-*cis*- and -*trans*-isomers were also measured by Dr. F. B. Strauss (Dyson Perrins Laboratory, Oxford) with a Perkin Elmer double-beam instrument, in cells of 0·01 and 0·1 mm. length.

These measurements show that the bands near 968 cm.$^{-1}$ have extinction coefficient $E\alpha/l$ of 2·5—2·7 in the *cis*- and 39 in the *trans*-series, where $E\alpha = \log I_0/I$ and $l$ is in mm.

Although no attempt was made to observe the variation of the spectra during purification to constant f. p., we assume that the very small bands of the *cis*-forms are peculiar to these compounds and are not due to the presence of *trans*-isomers.

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## 630. *Some Alkylquinoline-5 : 8-quinones.*

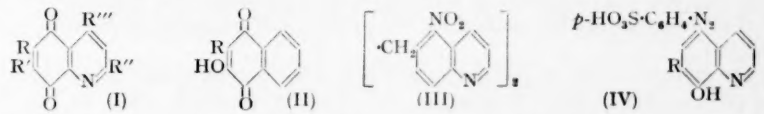
By R. Long and K. Schofield.

The synthesis from alkyl-amino- and alkyl-hydroxy-quinolines of 6- and 7-alkylquinoline-5 : 8-quinones, as far as the butyl compounds, is described.

The action of hydroxylamine and alkali on certain alkylnitroquinolines gave moderate to poor yields of alkyl-amino-nitroquinolines.

The bacteriostatic properties of the quinoline-5 : 8-quinones are reported.

Very few compounds of the type (I) have been described. Fischer and Renouf (*Ber.*, 1884, **17**, 1644) obtained quinoline-5 : 8-quinone, and Noelting and Trautmann (*Ber.*, 1890, **23**, 3671) prepared the monoximes of (I; R′ = R″ = R‴ = H, R = Me) and (I; R = R″ = R‴ = H, R′ = Me). By an indirect method Zincke and Muller (*Annalen*, 1891, **264**, 201) obtained (I; R″ = R‴ = H, R = OH, R′ = Cl), whilst more recently 6-methylquinoline-5 : 8-quinone was prepared and found to be almost devoid of antihæmorrhagic properties (Christiansen and Dolliver, *J. Amer. Chem. Soc.*, 1941, **63**, 1470; Ansbacher, *Proc. Soc. Exp. Biol. N.Y.*, 1941, **46**, 421). In the course of antitubercular studies Graef, Fredericksen, and Burger (*J. Org. Chem.*, 1946, **11**, 257) synthesised (I; R = R′ = H, R‴ = Me, R″ = $[CH_2]_{10}{\cdot}CO_2H$).




In view of the importance of naturally occurring naphtha-1 : 4-quinones, the known antimalarial properties of 2-alkyl-3-hydroxynaphtha-1 : 4-quinones (II) (Fieser and his co-workers, *J. Amer. Chem. Soc.*, 1948, **70**, 3151 *et seq.*), and the possible significance of quinonoid derivatives for the antimalarial action of certain quinoline compounds (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; Drake and Pratt, *J. Amer. Chem. Soc.*, 1951, **73**, 544; Elderfield, " Heterocyclic Compounds," Vol. IV, p. 198, Wiley, 1952), we undertook a study of quinoline-5 : 8-quinones. We describe here a number of 6- and 7-alkylquinoline-5 : 8-quinones.

Two routes to quinoline-5 : 8-quinones were examined. One proceeded from 5- or 8-aminoquinolines, the other from 5- or 8-hydroxyquinolines (in some cases obtained from the amines). The former method proved the better.

Satisfactory procedures for coupling benzenediazonium chloride with aminoquinolines were devised by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1920, **42**, 2278) and Renshaw, Friedman, and Gajewski (*ibid.*, 1939, **61**, 3322). The latter workers found 5-aminoquinoline to couple at both the 6- and the 8-position. Guided by this experience we coupled diazotised sulphanilic acid with a number of 6-alkyl-5- and 7-alkyl-8-aminoquinolines (Long and Schofield, *J.*, 1953, 2350) in acetic acid: in these cases *ortho*-coupling is impossible, and the *p*-amino-azo-compounds were obtained in almost quantitative yields. These products were reduced by stannous chloride to the corresponding 6- or 7-alkyl-5 : 8-diaminoquinolines, which were immediately oxidised with potassium dichromate. In this manner 2-, 6-, and 7-methyl-, 6- and 7-ethyl-, 6-propyl-, and 6- and 7-butyl-quinoline-5 : 8-quinone were readily obtained in yields varying from 27 to 75%. In an attempt to estimate the yields of diamines formed from the azo-compounds in the cases of the three monomethyl compounds, the solid products were isolated. As expected, these rapidly darkened, and after some months gave very poor yields of quinones by dichromate oxidation. The toluene-*p*-sulphonamido-derivatives of these diamines could only be obtained in poor yields.

It seemed that 5 : 8-diaminoquinolines, the immediate precursors of quinones in the above work, might be obtained by another method. Recently Huisgen (*Annalen*, 1947, **559**, 101) and Colonna and Montanari (*Gazzetta*, 1951, **81**, 744) obtained aminonitro-

quinolines in moderate to very good yields by the action of hydroxylamine and alkali on nitroquinolines (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273). By applying the conditions of Colonna and Montanari (*loc. cit.*) to 6-methyl-5-nitroquinoline, we obtained 8-amino-6-methyl-5-nitroquinoline (30—35%), unchanged starting material, and variable amounts of a sparingly soluble amorphous product. By varying the proportions of reactants it was possible to maintain the yield of nitro-amine, raise the recovery of starting material, and decrease the amount of amorphous material. We were not able to isolate a salt of the type described by Meisenheimer and Patzig (*Ber.*, 1906, **39**, 2533). Purification of the amorphous material gave a compound which from analysis, and by analogy with the experiments of Huisgen (*loc. cit.*), is possibly 1 : 2-di-(5-nitro-6-quinolyl)ethane (III). However, the action of methanolic potassium hydroxide on 6-methyl-5-nitroquinoline, hydroxylamine being absent, gave a different, unidentified product, evidently not encountered by Bogert and Fisher (*J. Amer. Chem. Soc.*, 1912, **34**, 1569) who described a similar reaction.

Whilst the above reaction provided a useful method of preparing 8-amino-6-methyl-5-nitroquinoline, its application to 6-ethyl-5- and 7-methyl-8-nitroquinoline gave only poor yields of the nitro-amines, and the method failed with 6-butyl-5-nitroquinoline. Since these are instances of nucleophilic substitution the generally adverse influence of alkyl groups is readily understood. 8-Amino-6-methyl- and 8-amino-6-ethyl-5-nitroquinoline were reduced to diamines, which were oxidised to quinoline-5 : 8-quinones. Having regard to the ready availability of 6-methyl-5-nitroquinoline, the sequence of reactions described represents a useful method for obtaining small quantities of 6-methylquinoline-5 : 8-quinone.

For the method based on hydroxyquinolines, 8-hydroxyquinoline is readily available, and the process of nitrosation (Lippmann and Fleissner, *Monatsh.*, 1889, **10**, 794) followed by treatment with iron filings and very dilute hydrochloric acid, whereby 5 : 8-dihydroxyquinoline is formed (Matsumara and Sone, *J. Amer. Chem. Soc.*, 1931, **53**, 1406), was recommended by Fieser and Martin (*ibid.*, 1935, **57**, 1840). However, like Moness and Christiansen (*J. Amer. Pharm. Assoc.*, 1934, **23**, 228) we found the product difficult to purify, and the large volume of reaction solution made the method impracticable.

Fischer and Renouf (*loc. cit.*) originally prepared quinoline-5 : 8-quinone by coupling 8-hydroxyquinoline with diazotised sulphanilic acid, reducing the resulting azo-compound, and oxidising 5-amino-8-hydroxyquinoline. Christiansen and Dolliver (*loc. cit.*) similarly obtained the 6-methylquinone from 5-hydroxy-6-methylquinoline. The method suffers from the inacessibility of homologues of 5- and 8-hydroxyquinoline. Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1944, **66**, 1166) prepared 5-hydroxy- from 5-amino-quinoline, but gave no experimental details. Our own experiments with 5-aminoquinoline, and also attempts to repeat Noelting and Trautmann's preparation of 5-hydroxy- from 5-amino-6-methylquinoline (*Ber.*, 1890, **23**, 3654), realised only poor yields of the hydroxy-compounds. 8-Hydroxy-7-methylquinoline is directly available (Long and Schofield, *loc. cit.*), but an attempt to prepare it from 8-amino-7-methylquinoline gave no phenolic material. Our experience in these experiments is similar to that of other workers (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 550; Price, Snyder, and Heyningen, *J. Amer. Chem. Soc.*, 1946, **68**, 2589; Fieser and Hershberg, *ibid.*, 1940, **62**, 1640; Cook, Heilbron, Hey, Lambert, and Spinks, *J.*, 1943, 404), which indicates difficulties in utilising diazotised aminoquinolines. We prepared 7-allyl-8-hydroxyquinoline by a slight modification of the method of Mander Jones and Trikojus (*Proc. Roy. Soc., N.S.W.*, 1932, **66**, 300), and by a similar process obtained 6-allyl-5-hydroxyquinoline from 5-hydroxyquinoline. The allyl compounds were reduced to hydroxy-propylquinolines.

With some simplification, Fischer and Renouf's method (*loc. cit.*) for preparation of quinoline-5 : 8-quinone from 8-hydroxyquinoline proved satisfactory. We describe below some experiments made to determine the effect of varying the amount of reagent used to oxidise the intermediate 5-amino-8-hydroxyquinoline. By similar procedures we also obtained 6- and 7-methyl- and 7-propylquinoline-5 : 8-quinone. Although 7-allyl-8-hydroxyquinoline readily coupled with diazotised sulphanilic acid and the resulting azo-compound appeared to be reduced normally, we could not obtain a quinone in this case.

Finally, 2 : 4-dimethylquinoline-5 : 8-quinone was obtained by demethylating 5 : 8-dimethoxy-2 : 4-dimethylquinoline and oxidising the product.

The quinolinequinones were yellow-brown crystalline compounds, with a characteristic pungent odour. In both the 6- and the 7-alkyl series the melting point decreased with increasing size of the alkyl group. 6-Butylquinoline-5 : 8-quinone decomposed rapidly in the air. The quinones were quickly decomposed by alkali.

| Compound (I) | Haemolytic *Streptococcus* | *Staph. aureus* | *B. coli* |
|---|---|---|---|
| R = R′ = R″ = R‴ = H | 0·5 | 5 | 20 |
| R′ = R″ = R‴ = H, R = Me | ,, | ,, | ,, |
| R = R″ = R‴ = H, R′ = Me | 0·02 | ,, | 10 |
| R′ = R″ = R‴ = H, R = Et | 20 | 30 | 50 |
| R = R″ = R‴ = H, R′ = Et | 10 | 30 | 100 |
| R′ = R″ = R‴ = H, R = Pr | 5 | 20 | 50 |
| R = R″ = R‴ = H, R′ = Pr | 0·05 | 5 | 50 |
| R = R″ = R‴ = H, R′ = Bu | 5 | 20 | 50 |
| R = R′ = R‴ = H, R″ = Me | 2 | >20 | >20 |
| (IV; R = allyl) | 20 | 20 | 50 |
| (IV; R = Pr) | ,, | ,, | >50 |
| 6-Methyl-5 : 8-di(toluene-*p*-sulphonamido)quinoline | >10 | >10 | >10 |
| 7-Methyl-5 : 8-di(toluene-*p*-sulphonamido)quinoline | >Saturated | >Saturated | >Saturated |

> indicates that the compound was not inhibitory in saturated solution at pH 7·5.

The bacteriostatic properties of a number of the above compounds were examined. For the tabulated figures, which are the concentrations in mg./100 c.c. which prevented visible growth in Hedley Wright broth overnight at 37°, we are indebted to Drs. A. T. Fuller and F. Hawking of the National Institute for Medical Research. It is interesting that 7-alkylquinoline-5 : 8-quinones are more active than the 6-isomers, and that an alkyl group with an odd number of carbon atoms produces a substantial increase in activity compared with even-numbered members. The high activity shown *in vitro* by some of the compounds was not maintained *in vivo* : neither the quinones nor the azo-compounds were effective against *P. berghei* or *T. equiperdum in vivo*.

## Experimental

The m. p.s (decomp.) of the quinones were determined by immersing the specimens in a bath about 20° below the approximately determined figure, and raising the temperature rapidly. Ethereal extracts were dried with anhydrous $Na_2SO_4$.

*Hydroxyquinolines.—5-Hydroxyquinoline.* 5-Aminoquinoline (28·5 g.) in hydrochloric acid (55 c.c. of concentrated acid in 100 c.c. of water) was treated with aqueous sodium nitrite (14 g. in 50 c.c.) at 0—5°. Much tar was formed. The solution was slowly added to boiling hydrochloric acid (300 c.c. of concentrated acid in 1 l. of water). Neutralisation with sodium carbonate gave a sludge which was extracted with ether. The red extract was decolorised with large quantities of charcoal. Removal of the ether left a white solid (2·5 g.), m. p. 218°.

*5-Allyloxyquinoline.* Allyl bromide (3·8 g.) was added dropwise to a stirred, refluxing solution of potassium (1·25 g.) and 5-hydroxyquinoline (4·5 g.) in absolute methanol (18 c.c.). Refluxing was continued for 5 hr., methanol was removed, sodium hydroxide solution was added, and the red solution was extracted with ether. Distillation of the crude product (3·9 g.) gave colourless *5-allyloxyquinoline* (3 g.), b. p. 120—124°/0·7 mm. (Found : C, 76·7; H, 6·6. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0%). The *picrate* formed yellow needles, m. p. 168—170° (Found : C, 52·7; H, 3·3. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%), from acetone. In a similar way 8-hydroxyquinoline (120 g.) gave 8-allyloxyquinoline (103 g.), b. p. 158—160°/2 mm.

*6-Allyl-5-hydroxyquinoline.* When the above ether (2 g.) was heated a purple-black colour developed which became progressively darker. At 200° rearrangement was complete. The product solidified on cooling, and trituration with ether gave *6-allyl-5-hydroxyquinoline* (1·8 g.), which formed needles, m. p. 161° (Found : C, 77·6; H, 5·8. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%), from methanol. The *picrate* formed yellow needles, m. p. 222° (decomp.) (Found : C, 51·9; H, 3·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%), from acetone–aqueous methanol. By the method of Mander Jones and Trikojus (*loc. cit.*) 8-allyloxyquinoline (47 g.) gave 7-allyl-8-hydroxyquinoline (45 g.), b. p. 120°/0·5 mm.

*5-Hydroxy-6-propylquinoline.* The allyl compound (0·7 g.), 5% palladium–charcoal (0·35 g.)

and methanol (20 c.c.) were shaken with hydrogen. Reaction was rapid, and filtration and concentration, followed by the addition of water, gave the substantially pure product (0·68 g.). From aqueous methanol *5-hydroxy-6-propylquinoline* formed plates, m. p. 178—179° (Found: C, 76·6; H, 7·1. $C_{12}H_{13}ON$ requires C, 76·9; H, 7·0%). Its *picrate* separated from acetone–aqueous methanol as fine yellow needles, m. p. 231° (decomp.) (Found: C, 52·3; H, 3·9. $C_{12}H_{13}ON,C_6H_3O_7N_3$ requires C, 52·0; H, 3·9%).

*8-Hydroxy-7-propylquinoline.* The allyl compound (30 g.), palladium–charcoal (3 g.) and methanol (300 c.c.) gave in the usual way *8-hydroxy-7-propylquinoline* (26·3 g.), b. p. 147—149°/5—6 mm. (Found: C, 77·0; H, 7·0%), which solidified at 0°. The *picrate* crystallised from methanol as yellow needles, m. p. 168—169° (Found: C, 52·6; H, 3·8%).

*Hydroxy-*p*-sulphophenylazoquinolines.*—(i) In preliminary experiments a vigorously stirred solution of the hydroxyquinoline in aqueous sodium hydroxide (1 equiv.) was treated with sulphanilic acid (1 equiv.) in hydrochloric acid (2 equivs.), and then a solution of sodium nitrite (1 equiv.) was added at 5°. Next morning the azo-compound was collected. In this way azo-compounds were obtained from 8-hydroxy- (100%), 5-hydroxy-6-methyl- (86%), and 8-hydroxy-7-methyl-quinoline (97%; in this case some alcohol was used to obtain complete dissolution of the hydroxyquinoline).

(ii) The hydroxyquinolines were more soluble in acid than in alkali, and in subsequent work we employed a mixture of an aqueous solution of sulphanilic acid with one of the quinoline in hydrochloric acid (1 equiv.). Frequently a crystalline suspension was formed at 5°, but this did not affect the diazotisation. The temperature of diazotisation was not critical, equal succcess being achieved at 20°. This method gave 90—98% yields of the azo-compound from 8-hydroxy-, *7-allyl-8-hydroxy-* [crimson needles (Found: C, 58·2; H, 4·5. $C_{18}H_{15}O_4N_3S$ requires C, 58·2; H, 4·1%) from pyridine], and *8-hydroxy-7-propyl-quinoline* [dark red needles (Found: C, 55·7; H, 4·6. $C_{18}H_{17}O_4N_3S,H_2O$ requires C, 55·5; H, 4·9%) from pyridine].

*Amino-*p*-sulphophenylazoquinolines.*—A solution of sulphanilic acid, sodium hydroxide, and sodium nitrite (1 equiv. of each) was poured into ice and hydrochloric acid (2 equivs.). The resulting suspension was immediately added to a vigorously stirred and cooled solution of the alkyl-aminoquinoline in dilute acetic acid. The dark red suspension was treated with sodium acetate. Next morning the purple solid was collected. Azo-compounds in 90—100% yield were thus obtained from 8-amino-2-methyl-, 5-amino-6-methyl-, 8-amino-7-methyl-, 5-amino-6-ethyl-, 8-amino-7-ethyl-, 5-amino-6-propyl-, 5-amino-6-butyl-, and 8-amino-7-butyl-quinoline.

*Quinoline-5 : 8-quinones.*

*From Hydroxy-*p*-sulphophenylazoquinolines.*—The azo-compound was added slowly to a boiling solution of stannous chloride (2·3 equivs.) in hydrochloric acid (2 c.c. of concentrated acid per 1 g. of stannous chloride). Boiling was continued until the initial colour had disappeared. Frequently yellowish-brown crystals separated. The mixture was diluted with boiling water, and hydrogen sulphide was passed in for several hours. After filtration the solution was oxidised directly.

Aliquot parts of the aminophenol solution were vigorously agitated with a solution of potassium dichromate in sulphuric acid (1 c.c. of concentrated acid and 10 c.c. of water per 1 g. of potassium dichromate). The resulting dark red solution was extracted with chloroform. Removal of the solvent provided the quinone. In the following Table the number of atom-equivs. of oxygen is calculated by assuming that the aminophenol was formed quantitatively.

| | Azo-compound (g.) | Aminophenol soln. (c.c.) | $K_2Cr_2O_7$ (g.) | Atom-equivs. of $O_2$ | Yield (g.) | Yield (%) |
|---|---|---|---|---|---|---|
| Quinoline-5 : 8-quinone [1] | 22·7 | 200 | 4·2 | 0·6 | 3·35 | 30 [2] |
| | ,, | ,, | 8·4 | 1·2 | 3·25 | 29·5 |
| | 56·2 | 3500 | 25·0 | 1·5 | 7·30 | 27 |
| | 68·1 | 1500 | 37·8 | 1·8 | 8·90 | 27 |
| | 22·7 | 400 | 16·8 | 2·4 | 3·3 | 30 |
| | ,, | 450 | 21·0 | 3·0 | 3·0 | 27 |
| 7-Propylquinoline-5 : 8-quinone [1] | 13·0 | 700 | 9·8 | 3·0 | 4·9 | 68 |
| | 4·6 | 250 | 4·5 | 3·7 | 1·4 | 55 |
| | ,, | 340 | 6·7 | 5·5 | 1·45 | 57 |
| | ,, | 400 | 7·4 | 8·9 | 1·5 | 58·5 |

[1] See below for properties. [2] This material was highly impure and rapidly decomposed.

In the same way 5-hydroxy-6-methyl-8-*p*-sulphophenylazoquinoline (2 g.) with potassium dichromate (4 g.) in 3N-sulphuric acid (50 c.c.), and 8-hydroxy-7-methyl-5-*p*-sulphophenylazo-

quinoline (5·15 g.) with potassium dichromate (5 g.), gave the corresponding quinones (0·38 g. and 1·37 g.) (see below).

| Quinoline-5 : 8-quinone | Azo-compound (g.) | Vol. of diamine soln. (l.) | $K_2Cr_2O_7$ (g.) | Atom-equivs. of $O_2$ | Yield (g.) | Yield (%) |
|---|---|---|---|---|---|---|
| 2-Methyl- ..... | 13·3 | 0·4 | 10·5 | 3·3 | 1·8 | 27 |
| 6-Methyl- ..... | ,, | ,, | 21·0 | 6·6 | 1·5 | 22 |
| 6-Methyl- ..... | 5·8 | 0·44 | 6·5 | 4·0 | 0·8 | 28 |
| | ,, | ,, | ,, | ,, | 1·0 | 34 |
| 7-Methyl- ..... | 11·5 | 0·4 | 9·8 | 3·0 | 2·6 | 45 |
| | 16·1 | 0·5 | 8·4 | 2·0 | 3·0 | 37 [1] |
| | ,, | 0·6 | 12·6 | 3·0 | 2·6 | 32 [1] |
| | ,, | 0·7 | 16·8 | 4·0 | 2·3 | 28 [1] |
| 6-Ethyl- ..... | 27·5 | 3·0 | 22·5 | 3·0 | 10·3 | 73 |
| 7-Ethyl- ..... | 6·7 | 1·0 | 5·3 | ,, | 2·4 | 68·5 |
| | 20·0 | 3·0 | 15·9 | ,, | 6·6 | 63·5 [2] |
| 6-Propyl- ..... | 6·2 | 1·0 | 3·2 | 2·0 | 1·7 | 50·5 |
| | ,, | ,, | 4·9 | 3·0 | 1·6 | 47·5 |
| | 18·6 | 3·0 | 14·7 | ,, | 2·7 | 27 [2] |
| 6-Butyl- ..... | 23·4 | 2·0 | 9·6 | 2·0 | 4·5 | 34 |
| 7-Butyl- ..... | 6·2 | 1·0 | 2·0 | ,, | 0·9 | 44 [2] |
| | ,, | ,, | 3·0 | 3·0 | 1·15 | 56 [2] |
| | 18·5 | 3·0 | 9·0 | ,, | 4·6 | 75 |

[1] Experiments with an old specimen of diamine hydrochloride. [2] In these experiments a brownish-black colour was produced in the drying agent when the chloroform extract was dried. The specimen of $Na_2SO_4$ used proved to be slightly alkaline.

| Quinoline-5 : 8-quinone | Method of prepn.[1] | Solvent [2] | Cryst. form | M. p. | Formula | Analysis, % Found C | Found H | Reqd. C | Reqd. H |
|---|---|---|---|---|---|---|---|---|---|
| Parent compound | A | a | Brown needles | 113—115° (decomp.) [3] | — | — | — | — | — |
| 2-Methyl- | B | ,, | Light brown needles | 135 (decomp.) | $C_{10}H_7O_2N$ | 69·5 | 4·15 | 69·4 | 4·1 |
| 6-Methyl- | A & B | ,, | Brown needles | 177—180 (decomp.) [4] | ,, | 69·9 | 4·1 | ,, | ,, |
| 7-Methyl- | ,, | ,, | Pale yellow rods | 175—180 (decomp.) | ,, | 69·3 | 4·1 | ,, | ,, |
| 2 : 4-Dimethyl- | C | ,, | Yellow-brown needles | 156 (decomp.) | $C_{11}H_9O_2N$ | 70·4 | 4·9 | 70·6 | 4·85 |
| 6-Ethyl- | B | ,, | Yellow-brown flakes | 135—137 (decomp.) | ,, | 70·3 | 4·7 | ,, | ,, |
| 7-Ethyl- | ,, | ,, | Brown prisms | 123—125 (decomp.) | ,, | 70·4 | 5·3 | ,, | ,, |
| 6-Propyl- | ,, | b | Brown feathers | 68—70 | $C_{12}H_{10}O_2N$ | 71·5 | 6·0 | 71·6 | 5·5 |
| 7-Propyl- | A | a | Ochre crystals | 75—78 | ,, | 70·7 | 4·9 | ,, | ,, |
| 6-Butyl | B | b | Fawn powder | 49—50 [5] | $C_{13}H_{13}O_2N$ | 71·1 | 5·7 | 72·5 | 6·15 |
| 7-Butyl- | B | ,, | Greenish-brown | 67—88 | ,, | 72·5 | 5·6 | ,, | ,, |

[1] (A) From hydroxyquinolines. (B) From aminoquinolines. (C) See separate description. [2] (a) Benzene–ligroin (b. p. 60—80°); (b) ether–light petroleum (b. p. 40—60°). [3] Fischer and Renouf (*loc. cit.*) gave m. p. 110—120° (decomp.). [4] Christiansen and Dolliver (*loc. cit.*) gave m. p. 167—168°. [5] This compound decomposed rapidly in air.

*From Amino-*p*-sulphophenylazoquinolines.*—The azo-compounds were reduced in the way described above. Except in the cases of the three monomethyl compounds, the solutions were partly freed from tin and oxidised immediately. When the diluted reduction solution from 5-amino-6-ethyl-8-*p*-sulphophenylazoquinoline was treated with hydrogen sulphide and filtered, the filtrate was colourless. The tin sulphide contained small red crystals, and repeated extraction with boiling water gave the characteristic red diamine solution. Subsequently, all sulphide residues were similarly treated. Details of these experiments and of the *products* are tabulated above.

The residues obtained by evaporating hydrochloric acid solutions of 5 : 8-diamino-2- and -6-methylquinoline were dissolved in pyridine and treated with toluene-*p*-sulphonyl chloride. Much heat was evolved, and next morning the solutions were poured into iced hydrochloric acid. The solutions of the precipitates in aqueous sodium hydroxide were decolorised and acidified. 2-*Methyl-*, prisms, m. p. 194° (Found : C, 59·6; H, 4·8. $C_{24}H_{23}O_4N_3S_2$ requires C, 59·6; H, 4·8%), and 6-*methyl*-5 : 8-*di*(*toluene*-p-*sulphonamido*)*quinoline*, small needles, m. p. 186° (Found : C, 59·75; H, 4·9%), from aqueous methanol, were obtained.

*Miscellaneous experiments.*

*Reaction of 6-Methyl-5-nitroquinoline with Hydroxylamine.*—The best yield of 8-amino-6-methyl-5-nitroquinoline was obtained as follows : The nitro-compound (11·5 g.), hydroxylamine hydrochloride (50 g.), and absolute alcohol (200 c.c.) were stirred and refluxed whilst a solution of potassium hydroxide (100 g.) in absolute alcohol (500 c.c.) was added slowly. Refluxing was continued for 6 hr. The mixture was poured on ice and the product was collected next morning. The solid was repeatedly extracted with benzene, and on cooling of the concentrated extracts the amine (5·3 g.; m. p. 190—192°) separated. *8-Amino-6-methyl-5-nitroquinoline* formed short, orange-red needles, m. p. 192—193° (Found : C, 58·8; H, 4·2. $C_{10}H_9O_2N_3$ requires C, 59·0; H, 4·5%), from benzene. The *semipicrate* formed orange needles, m. p. 177—180° (decomp.) (Found : C, 48·1; H, 3·4. $C_{10}H_9O_2N_3,\frac{1}{2}C_6H_3O_7N_3$ requires C, 49·1; H, 3·3%).

In another experiment, carried out similarly but at 70° for 3 hr., the nitroquinoline (2 g.), hydroxylamine hydrochloride (5 g.), potassium hydroxide (10 g.), and absolute alcohol (140 c.c.) gave, as the sole product, benzene-insoluble material (1·3 g.; m. p. 282—283°). Recrystallised from acetic anhydride this formed soft, pale yellow-green needles, m. p. 282—285° (Found : C, 63·1; H, 3·5; N, 12·2. $C_{20}H_{14}O_4N_4$ requires C, 64·1; H, 3·8; N, 15·0%). Various conditions gave mixtures of starting material, nitro-amine, and amorphous material (for details see R. Long, Thesis, London, 1953).

*Action of Alkali on 6-Methyl-5-nitroquinoline.*—The nitro-compound (1 g.), potassium hydroxide (2 g.), and alcohol (20 c.c.) were refluxed for 2·5 hr. A dark brown colour was immediately produced, and small crystals (0·4 g.), m. p. 277—278°, separated. These were collected after the addition of water. From acetic anhydride the product formed golden needles, m. p. 312—315° (decomp.) (Found : C, 71·1; H, 2·9%). The same material (Found : C, 71·8; H, 3·1%) appeared to arise on crystallisation from a large volume of benzene.

*5 : 8-Diamino-6-methylquinoline and its Oxidation.*—8-Amino-6-methyl-5-nitroquinoline (3 g.), palladium–charcoal (0·5 g.), and warm methanol (500 c.c.) were shaken with hydrogen. Reduction was complete only after 2 days. Filtration and evaporation gave a greenish-black residue (2·6 g.), which from benzene formed golden blades of *5 : 8-diamino-6-methylquinoline*, m. p. 161—163° (Found : C, 68·3; H, 6·3. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4%). Its *picrate* crystallised from methanol–acetone as felted, tan needles, m. p. 197—200° (decomp.) (Found : C, 49·1; H, 3·8. $C_{10}H_{11}N_3,C_6H_3O_7N_3,C_3H_6O$ requires C, 49·6; H, 4·4%). The crude diamine (2 g.) in 6N-sulphuric acid (60 c.c.) gave, in the usual way with potassium dichromate (6·8 g. in 70 c.c. of water), 6-methylquinoline-5 : 8-quinone (0·5 g.).

The nitro-amine (8 g.), with stannous chloride (27·2 g.) and concentrated hydrochloric acid (56 c.c.) at 95° for 3 hr. gave a crystalline salt, which when dissolved in water (2·5 l.) and oxidised with potassium dichromate (24 g. in 275 c.c. of 4N-sulphuric acid) provided the quinone (3·55 g.).

*5-Amino-7-methyl-8-nitroquinoline.*—7-Methyl-8-nitroquinoline (5 g.), hydroxylamine hydrochloride (20 g.), and absolute ethanol (200 c.c.) were refluxed and treated slowly with potassium hydroxide (40 g.) in ethanol (200 c.c.). After refluxing for 8 hr. the mixture was poured into water, and the precipitate (3·6 g.) collected. This material (2·5 g.) was repeatedly crystallised from benzene, *5-amino-7-methyl-8-nitroquinoline* being obtained as yellowish-orange prisms (0·55 g.), m. p. 207—208° (Found : C, 58·9; H, 4·55. $C_{10}H_9O_2N_3$ requires C, 59·0; H, 4·5%).

*8-Amino-6-ethyl-5-nitroquinoline.*—In the same way 6-ethyl-5-nitroquinoline (10 g.), hydroxylamine hydrochloride (40 g.), and absolute ethanol (100 c.c.) gave with potassium hydroxide (80 g.) in absolute ethanol (200 c.c.) a crude product (2·95 g.) which could not be purified by crystallisation. Passage in benzene over alumina gave a bright orange middle band of *8-amino-6-ethyl-5-nitroquinoline* (1·1 g.) which formed crimson needles, m. p. 128—129° (Found : C, 60·9; H, 4·7. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1%), from ether.

The nitro-amine (0·4 g.), with palladium–charcoal (0·1 g.) in methanol (10 c.c.), was very slowly reduced. The crude diamine so obtained, in 4N-sulphuric acid (10 c.c.), was oxidised with potassium dichromate (0·5 g.) in water (10 c.c.), giving 6-ethylquinoline-5 : 8-quinone (0·25 g.).

*5 : 8-Dimethoxy-2 : 4-dimethylquinoline.*—2 : 5-Dimethoxyaniline (18 g.) and acetylacetone (13 g.) were refluxed for ½ hr., after which concentrated sulphuric acid (0·5 c.c.) was added carefully. After ¼ hr. more of refluxing the mixture was poured into concentrated sulphuric acid (150 c.c.), and the solution was warmed at 95° for ¼ hr. The cooled, diluted solution was basified, and the precipitate crystallised from ethyl acetate, giving crystals (6 g.), m. p. 104—107° (Lions, Perkin, and Robinson gave m. p. 107°).

*2 : 4-Dimethylquinoline-5 : 8-quinone.*—The above product (1 g.) and hydrobromic acid (*d* 1·48; 5 c.c.) were refluxed for 5 hr. The suspension formed on cooling was diluted and

neutralised with ammonia, and extracted with ether. The tacky product recovered from the ether was treated in 5N-hydrochloric acid (10 c.c.) with excess of aqueous ferric chloride solution (10%). From the deep-red solution chloroform removed **2 : 4-*dimethylquinoline*-5 : 8-*quinone*** (0·35 g.) (see Table).

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## 631. *Adaptive Behaviour of Coliform Bacteria to Certain Sugars.*

By N. M. MIMS and SIR CYRIL HINSHELWOOD.

Adaptation of a strain of *Bact. coli* to a cellobiose–ammonium sulphate medium and its complete adaptation to a corresponding glucose medium appear to be processes partially linked.

When *Bact. lactis aerogenes* is transferred between media containing glucose and inositol severally as carbon sources two types of behaviour are observable. In one, optimum adaptation to the two sugars can be held simultaneously; in the other, the two kinds of adaptation are to some extent incompatible and competitive.

THE object of the experiments to be described was to clarify further the facts about the relations between the adaptive responses of bacteria to different carbon sources. Sometimes optimum-growth characteristics in one medium are quite compatible with those in another; sometimes two kinds of adaptation are incompatible and competitive, but the behaviour is of some complexity.

A preliminary investigation was carried out on the behaviour of several strains in inositol and cellobiose media, and the following two examples chosen for further study: (i) behaviour of *Bact. coli* (described as strain P34Type 1) in glucose and cellobiose media, and (ii) behaviour of *Bact. lactis aerogenes* in glucose and inositol media.

(i) *Behaviour of* Bact. coli *strain P34 Type 1 in Glucose and Cellobiose Media.*—The strain was transferred from nutrient broth to glucose to which asparagine in small quantity had been added. Subsequently it was subcultured daily in the glucose synthetic medium in the absence of asparagine. This medium contained, besides the carbon source, ammonium sulphate, magnesium sulphate, and phosphate buffer. After 20 subcultures in the glucose medium, when the mean generation time (the time taken for cell numbers to double in the logarithmic growth phase) was approximately stable, the strain was inoculated into a cellobiose medium and its mean generation time in this sugar measured at intervals; serial subculture in the glucose medium was also continued, and the mean generation time of the strain determined after every few subcultures. Experimental methods were as described in *J.*, 1938, 1930; 1939, 1683; 1943, 208; 1953, 663. At intervals the bacteria which had been transferred to cellobiose were re-transferred to glucose, and their mean generation time was determined. Fig. 1 shows the results obtained.

The mean generation times in the glucose cultures uninterrupted by passage through cellobiose remained fairly constant until the 48th subculture when the value fell by approximately 20%. The strain on first cultivation in cellobiose (after 20 subcultures in glucose) showed a mean generation time of 360 min., which during the next seven subcultures in this sugar fell rapidly to a value of 40 min., and then did not alter on repeated cultivation.

The mean generation time re-measured in glucose after a number of intervening passages through cellobiose fell together with that in cellobiose itself to a low and stable value. As usual it was reproducible and definite, and is the best general criterion of

bacterial growth rate. The value for the strain in glucose itself, however, did not reach a value of 40 min. until the 50th subculture in this sugar, but on subsequent passage through cellobiose it too fell to the same figure. From this it appears that there can be some change in the organisation of the cell which results in a more rapid reduction in the glucose

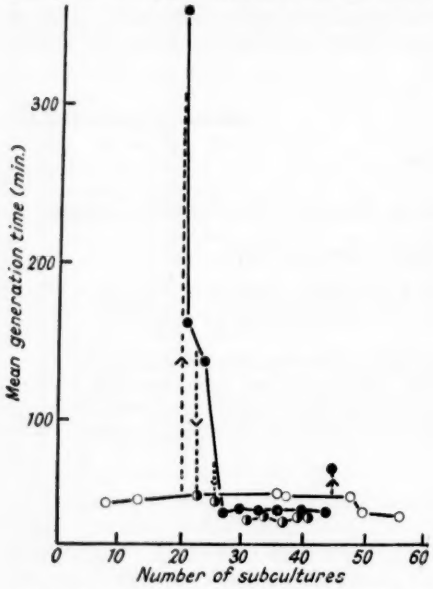



FIG. 1. Bact. coli *in glucose and cellobiose.*

○ *M.g.t. in glucose.*
● *M.g.t. in cellobiose.*
◑ *M.g.t. in glucose after intervening passages through cellobiose.*

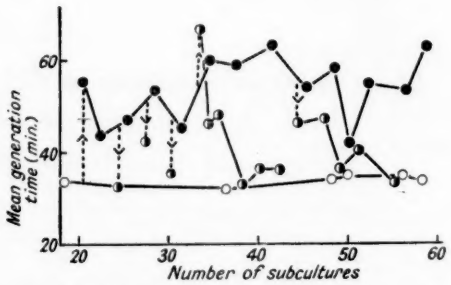



FIG. 2. Bact. lactis aerogenes *in glucose and inositol.*

○ *M.g.t. in glucose.*
● *M.g.t. in inositol.*
◑ *M.g.t. in glucose after intervening passages through inositol.*

FIG. 3.

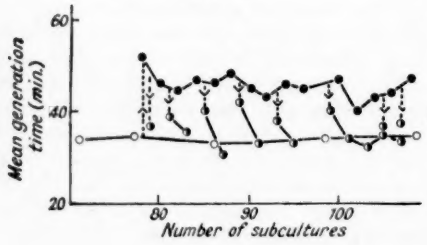
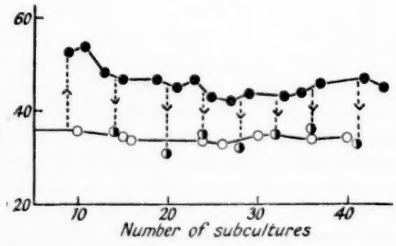



FIG. 4.




FIGS. 3 and 4. Bact. lactis aerogenes *in glucose and inositol.*

○ *M.g.t. in glucose.* ● *M.g.t. in inositol.*
◑ *M.g.t. in glucose after intervening passages through glucose.*

*Continuous lines show serial subculture in the carbon source in question. Discontinuous lines show points at which transference is made from one carbon source to another.*

mean generation time than would have occurred had the bacteria not been cultivated in the other sugar.

Since the mean generation time in glucose and that in cellobiose appear to be related to one another and since the mean generation time in glucose falls eventually to a stable value, it is expected that upon repeated passage through glucose efficient utilisation of cellobiose will become characteristic of the strain. In support of this it is observed that after 45 passages through glucose (just before the glucose mean generation time decreases)

the mean generation time of the strain on first cultivation in cellobiose is 68 min., which is considerably below the value of 360 min. obtained at an earlier stage in the passage through glucose.

(ii) *Behaviour of* Bact. lactis aerogenes *in Glucose and Inositol Media.—Bact. lactis aerogenes* was transferred from nutrient broth to a glucose synthetic medium and after a number of serial subcultures was inoculated into inositol. The mean generation time was measured at intervals in this medium, and also in glucose into which it was reinoculated from the inositol from time to time. The strain was also maintained in glucose and the mean generation time determined every few subcultures.

The mean generation time in glucose remained relatively steady at 33—37 min. At the 20th subculture the strain was inoculated into inositol and during repeated subculture the mean generation time fluctuated between 43 and 64 min. When the strain was reinoculated back into glucose after passage through inositol, it was found that the mean generation time was considerably higher than for cultures which had not passed through inositol (*i.e.*, passage through inositol had impaired growth in glucose). On repeated subculture in the glucose, however, this sub-optimal growth rate was restored to its normal value (see Fig. 2).

After 78 serial daily subcultures in glucose the strain was again transferred to inositol and the same procedure followed. In this case (Fig. 3) the fluctuations were smaller than in the earlier test, being in the range 40—52 min., and the loss in efficiency in the glucose utilisation, after passage through inositol, also less.

The whole series was later repeated in order to obtain more information about this apparent incompatibility of optimum adaptation to glucose and inositol. The same strain of *Bact. lactis aerogenes*, which had been maintained in nutrient broth in the meantime, was transferred to the glucose synthetic medium and the procedure of the earlier experiments again followed. Fig. 4 shows the results obtained. In this case very little fluctuation was observed after the first two subcultures, and the passage through inositol did not result in a decrease in the efficiency of utilisation of the glucose. There was found to be no difference in the characteristics of this series when subcultured every 12 hr. It was thought possible that the large fluctuation in the mean generation time in inositol, first observed, might be due to variations in the amount of iron in the medium, this metal having been found in some cases to have an effect on growth rate. The addition of the iron in this case should remove the fluctuation. It was found, however, that when the amount of iron was controlled at about $2\frac{1}{2}$ parts per million there was no change in behaviour.

From this it appears that *Bact. lactis aerogenes* can show two distinct types of behaviour: one where growth in inositol is incompatible with optimum growth in glucose and another where the two are compatible. It appears almost certain from a study of Figs. 2, 3, and 4 that the existence of the fluctuations in inositol is related to the modification of the properties in glucose.

The experiments were repeated after fresh cultivation of the strain in broth in order to ascertain whether, after growth in a medium containing a full complement of foodstuffs, the incompatible behaviour might again be observed on transfer of the strain to glucose and then to inositol. Complete compatibility was, however, again observed.

## Discussion

These results could doubtless be translated into suitable assumptions about successive mutations in both directions and about relative growth rates of mutant and non-mutant types. Some of the assumptions would, however, not be very probable. A continuous series of successive linked mutations would have to occur leading to more efficient utilisation of glucose and cellobiose by the *Bact. coli* strain.

It is at least a tenable opinion that the alternative is more probable, namely, that training to cellobiose involves a general reorganisation of the enzyme system of the cell, which is not only compatible with optimum growth in glucose but actually hastens its attainment. This matter will not be debated in detail here, since, on the one hand, the issue of mutation and adaptation is best settled by other arguments and, on the other

hand, the immediate object of this paper is simply to add to our descriptive knowledge of what might be called the adaptive patterns of bacterial strains. The example of the *Bact. coli* strain with cellobiose and glucose belongs to the class where there is an ultimate complete compatibility of two types of adaptation.

The example of the *Bact. lactis aerogenes* with glucose and inostiol shows that in some circumstances optimum behaviour in one sugar may be incompatible with that in another. But this was not consistently so.

In order to explain why a given strain of bacteria shows more than one type of behaviour it is again neither necessary nor profitable to consider the problem in terms of a complexity of assumed mutations and back-mutations. The variation in the conditions in a broth culture can result in a variation in the properties of the strain of bacteria dependent upon their history. Now the only difference between the bacteria showing the first type of behaviour (Fig. 2) and those showing the second (Fig. 4) is their time of cultivation in nutrient broth, and the difference in the response to cultivation in inositol must be due to the culture in the broth.

The difference in behaviour probably arises when varying conditions in the nutrient-broth cultures affect the enzyme balance of the cells to different degrees. The properties of the strain are determined by the particular enzyme balance in the cells at the time of their transfer from the nutrient broth to the synthetic medium.

Upon long repeated passage through glucose the bacteria became more stable in their behaviour, smaller fluctuations and a lower degree of incompatibility being observed. Thus the compatible type seems to be the more stable of the two conditions. It is probable that, since a change from incompatible to compatible behaviour occurs on repeated cultivation in glucose, the incompatible type is associated with some degree of unbalance in the enzyme equilibrium of the cell brought about by conditions in the broth cultures.

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## 632. *Syntheses of Methyl Ethers of Fructose.*

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3 : 4 : 6-, 1 : 4 : 6-, 1 : 3 : 4-, and 1 : 4 : 5-tri-*O*-methyl-, 3 : 4- and 4 : 5-di-*O*-methyl-, and 4-*O*-methyl-D-fructoses have been synthesised from one of the crystalline compounds 2 : 3-4 : 5- or 1 : 2-4 : 5-di-*O*-*iso*propylidene-D-fructose or from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose. The constitutions of these three *iso*propylidene derivatives are well established.

THREE crystalline substances whose constitutions have been established previously have been used as starting materials in this work. 1 : 2-4 : 5-, 2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose (D. J. Bell, *J.*, 1947, 1463) and 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (Morgan and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 1023).

Montgomery (*J. Amer. Chem. Soc.*, 1934, **56**, 419) synthesised 3 : 4 : 6-tri-*O*-methylfructose from crystalline 2 : 3-4 : 5-di-*O*-*iso*propylidenefructose by the formation of the 1-benzoyl derivative. In the present synthesis treatment of 2 : 3-4 : 5-di-*O*-*iso*propylidene-D-fructose with toluene-*p*-sulphonyl chloride gave crystalline 2 : 3-4 : 5-di-*O*-*iso*propylidene-1-*O*-toluene-*p*-sulphonyl-D-fructose. Removal of the *iso*propylidene residue followed by conversion into the fructofuranoside led to the isolation of a non-reducing syrup which partly crystallised. Methylation, removal of the toluene-*p*-sulphonyl residue, and hydrolysis gave 3 : 4 : 6-tri-*O*-methylfructose which was characterised by conversion into the crystalline methyl 3 : 4 : 6-tri-*O*-methyl-D-fructuronamide and also by oxidation to crystalline 2 : 3 : 5-tri-*O*-methyl-D-arabonolactone.

1 : 4 : 6-Tri-*O*-methylfructose was synthesised by Montgomery (*loc. cit.*), but only the rotation in chloroform was recorded. In the present work this trimethyl ether has been

synthesised from 1 : 2-4 : 5-di-*O*-*iso*propylidenefructose by blocking position 3 with a toluene-*p*-sulphonyl residue. Removal of the *iso*propylidene group and subsequent glycoside formation and methylation followed by reductive fission of the toluene-*p*-sulphonyl group and hydrolysis gave 1 : 4 : 6-tri-*O*-methylfructose as a chromatographically pure syrup.

An alternative synthesis was achieved from crystalline 2 : 3-*O*-*iso*propylidenefructose, obtained by the removal of the toluene-*p*-sulphonyl residues from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonylfructose. Methylation and hydrolysis gave 1 : 4 : 6-tri-*O*-methyl-D-fructose as a chromatographically pure, mobile syrup, identical with the 1 : 4 : 6-tri-*O*-methylfructose obtained from the former synthesis. 4 : 6-Di-*O*-methylfructuronic acid was obtained on oxidation.

Synthesis of 1 : 3 : 4-tri-*O*-methylfructose was achieved by the conversion of methyl 1-*O*-toluene-*p*-sulphonyl-D-fructofuranoside into the 6-*O*-trityl derivative. Removal of the toluene-*p*-sulphonyl residue followed by methylation gave methyl 1 : 3 : 4-tri-*O*-methyl-6-*O*-tritylfructoside. Hydrolysis of the trityl and glycosidic methoxyl groups gave 1 : 3 : 4-tri-*O*-methylfructose as a syrup which partly crystallised. The mother liquors were freed from 1 : 3 : 4 : 6-tetra-*O*-methylfructose by passage through silica gel (Bell and Palmer, *J.*, 1949, 2522).

Neither the isolation nor the synthesis of 1 : 4 : 5-trimethylfructose has been reported previously. Preferential hydrolysis of 2 : 3-4 : 5-di-*O*-*iso*propylidene-D-fructose gave crude 2 : 3-*O*-*iso*propylidene-D-fructopyranose. This was purified by conversion into the crystalline 1 : 4 : 5-tri-*O*-acetyl-2 : 3-*O*-*iso*propylidene-D-fructose. Hydrolysis of the acetyl groups followed by methylation and removal of the *iso*propylidene residue gave 1 : 4 : 5-tri-*O*-methyl-D-fructose, as a mobile syrup.

Macdonald and Jackson (*J. Res. Nat. Bur. Stand.*, 1940, **24**, 181) prepared syrupy 3 : 4-dimethylfructose from di-D-fructofuranose 2 : 1′-2′ : 1-di-anhydride and reported the isolation of a difficultly crystallisable osazone, m. p. 126°, but no other data or constants were recorded. In the present work methyl 1-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-D-fructoside was methylated and the product on reduction, detritylation, and hydrolysis gave a mixture of 3 : 4-di-*O*-methyl- and 3 : 4 : 6-tri-*O*-methyl-D-fructose, which was separated on cellulose.

3 : 4-Di-*O*-methylfructose has also been synthesised by the removal of the *iso*propylidene residue from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose with methanolic hydrogen chloride followed by methylation of the derived glycoside. Reduction and hydrolysis gave 3 : 4-di-*O*-methyl-D-fructose which was again purified from traces of trimethylfructose by separation on cellulose. The constants of the 3 : 4-di-*O*-methylfructose from the two syntheses were in good agreement and the two syrups were chromatographically identical. 3 : 4-Di-*O*-methylfructose was characterised by oxidation and conversion of the product into crystalline (−)-dimethoxysuccinamide and the bismethylamide.

No previous record of the synthesis of 4 : 5-di-*O*-methylfructose could be found. Crystalline 1 : 2-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-fructose was prepared from the 1 : 2-4 : 5-di-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl derivative by preferential hydrolysis of the *iso*propylidene residue (Ohle and Just, *Ber.*, 1935, **68**, 601). Methylation followed by reduction gave crystalline 4 : 5-di-*O*-methyl-1 : 2-*O*-*iso*propylidenefructose, and subsequent hydrolysis gave crystalline 4 : 5-di-*O*-methylfructose. A crystalline 2 : 5-dichlorophenylhydrazone and a phenylosazone were prepared.

4-*O*-Methylfructose has been isolated previously from di-D-fructofuranose 2 · 3′-2′ : 1-dianhydride (Macdonald and Jackson, *loc. cit.*) and was identified by the formation of a crystalline osazone, m. p. 156°. In the present work methylation of crystalline 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose gave crystalline 4-*O*-methyl-2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose. Reduction and hydrolysis led to the isolation of chromatographically pure syrupy 4-*O*-methylfructose. A crystalline osazone, m. p. 158°, identical with 4-*O*-methylglucosazone, was prepared. 4-*O*-Methylfructose was characterised by the same method as for 3 : 4-di-*O*-methylfructose; crystalline-D$_g$-*threo*-2-hydroxy-3-methoxysuccinamide and the bismethylamide were isolated.

## Experimental

All solvents were removed under reduced pressure and below 50°. The solvents used for elution, unless otherwise stated, were (I) *n*-butanol–ethanol–water (4 : 1 : 5) and (II) benzene–ethanol–water (167 : 47 : 15). Amberlite resins were used throughout.

3 : 4 : 6-*Tri*-O-*methylfructose*.—2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose, prepared from D-fructose (100 g.) according to the conditions used by Bell (*loc. cit.*), formed transparent needles (105 g., 73%) [from light petroleum (b. p. 60—80°)], m. p. 96—97°, $[\alpha]_D^{16}$ −34·1° (*c*, 5·6 in $CHCl_3$). To a solution of the crystals (82 g.) in dry pyridine (500 c.c.) finely powdered toluene-*p*-sulphonyl chloride (140 g.) was added during 2 hr. The 2 : 3-4 : 5-di-*O*-*iso*propylidene-1-*O*-toluene-*p*-sulphonyl-D-fructose (*A*) (115 g., 88%), isolated in the usual way (Percival and Zobrist, *J.*, 1952, 4306), had m. p. 82°, $[\alpha]_D^{16}$ −26° (*c*, 1·8 in MeOH) (cf. Ohle and Koller, *Ber.*, 1924, **57**, 1566, who record m. p. 83°, $[\alpha]_D^{19}$ −27° in EtOH) (Found: C, 54·7; H, 6·1; S, 7·5. Calc. for $C_{19}H_{26}O_8S$: C, 55·05; H, 6·3; S, 7·8%).

The crystals (*A*) (30 g.) were dissolved in ethanol (50 c.c.), and water (50 c.c.) was added until the solution became slightly turbid. Cation-exchange resin (40 g.) (IR-100 H) was added and the mixture refluxed with vigorous stirring (Glen, Myers, and Grant, *J.*, 1951, 2570) to complete dissolution (20 hr.). Filtration and neutralisation of the filtrate by shaking it with anion-exchange resin (IR-4B) (5 g.) for 2 hr. and removing the solvent gave 1-O-*toluene*-p-*sulphonyl*-D-*fructose* (*B*) (22·6 g., 93%), $[\alpha]_D^{17}$ −23° (*c*, 0·8 in MeOH) (Found: S, 9·1. $C_{13}H_{18}O_8S$ requires S, 9·5%). The syrup (*B*) (13·8 g.), dissolved in methanolic hydrogen chloride (1%; 500 c.c.), was kept at 25° for 100 hr., the maximum rotation ($[\alpha]_D$ +3°) having then been attained. (Further treatment led to a decrease in rotation and the formation of the pyranoside.) Isolation in the usual manner gave *methyl* 1-O-*toluene*-p-*sulphonylfructoside*, a syrup (*C*) (9·0 g., 63%), $[\alpha]_D^{18}$ +16° (*c*, 1·5 in MeOH) (Found: S, 8·6. $C_{14}H_{20}O_8S$ requires S, 9·2%). When kept this syrup partly crystallised; the crystals had m. p. 79—81°, $[\alpha]_D^{18}$ +15·2° (*c*, 1·0 in MeOH) (Found: C, 48·8; H, 5·6; S, 8·7. $C_{14}H_{20}O_8S$ requires C, 48·3; H, 5·8; S, 9·2%). Fivefold methylation of this derivative (9·0 g.) with methyl iodide and silver oxide gave *methyl* 3 : 4 : 6-*tri*-O-*methyl*-1-O-*toluene*-p-*sulphonylfructoside* (8·3 g., 82%), $[\alpha]_D^{18}$ +32° (*c*, 1·2 in MeOH) (Found: OMe, 31·8; S, 8·4. $C_{17}H_{26}O_8S$ requires OMe, 32·8; S, 8·5%). This syrup (8·3 g.), dissolved in methanol (140 c.c.), and water (75 c.c.) added to cause slight turbidity, was treated with sodium amalgam (4%; 200 g.) at 40—45° with vigorous stirring for 17 hr. The filtered solution was extracted with chloroform, and the chloroform extract dried ($Na_2SO_4$), saturated with carbon dioxide (to pH 7), and filtered. Evaporation and distillation at 120°/0·03 mm. gave methyl 3 : 4 : 6-tri-*O*-methyl-D-fructoside as a mobile syrup (4·55 g.), $[\alpha]_D^{19}$ +67·6° (*c*, 1·05 in MeOH) (Found: OMe, 51·8. Calc. for $C_{10}H_{20}O_6$: OMe, 52·8%). This furanoside (4·45 g.) was hydrolysed to 3 : 4 : 6-tri-*O*-methylfructose by 0·1N-sulphuric acid (250 c.c.) at 95° for 2·5 hr. (whereafter the rotation remained constant). A syrup (*D*) (3·91 g.) was obtained having $n_D^{18}$ 1·4661, $[\alpha]_D^{18}$ +27° (initial); +29° (24 hr.) (*c*, 1·4 in $H_2O$) (Found: C, 47·9; H, 8·1; OMe, 41·1. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2; OMe, 41·9%). Chromatographic analysis produced a single spot, $R_G$ 0·89 in solvent (I) and 0·75 in solvent (II).

*Characterisation of* 3 : 4 : 6-*Trimethyl*-D-*fructose*.—(a) *Oxidation with nitric acid followed by barium permanganate*. The syrup (*D*) (0·201 g.) was oxidised with nitric acid (2·5 c.c.; *d* 1·42) (Mullan and Percival, *J.*, 1940, 1505). The syrup (*E*) finally obtained was dried with anhydrous methanol and esterified with boiling methanolic hydrogen chloride (4%; 7 c.c.) for 17 hr. The derived amide (0·048 g.) had m. p. 98—100° (from ether) and showed no depression on admixture with authentic methyl 3 : 4 : 6-tri-*O*-methyl-D-fructuronamide (Found: C, 47·8; H, 7·4; N, 5·5. Calc. for $C_{10}H_{19}O_6N$: C, 48·2; H, 7·7; N, 5·6%).

3 : 4 : 6-Tri-*O*-methyl-D-fructuronic acid (*E*) (0·182 g.) was oxidised with barium permanganate according to the conditions described by Avery, Haworth, and Hirst (*J.*, 1927, 2317). The light petroleum extracts yielded a syrup which after distillation at 90°/0·003 mm. gave crystals (0·052 g.), m. p. 30—31°, $[\alpha]_D^{18}$ +44·8° ⟶ 24·0° (24 days) (*c*, 0·96 in $H_2O$) (Avery, Haworth, and Hirst, *loc. cit.*, record m. p. 32—33°, $[\alpha]_D$ +44·5° ⟶ 25·5°, for 2 : 3 : 5-tri-*O*-methylarabonolactone).

(b) *Oxidation with periodate*. To a solution of 3 : 4 : 6-tri-*O*-methylfructose (*D*) (0·19 g.) in water (10 c.c.), sodium metaperiodate solution (0·3M; 15 c.c.) was added and the solution set aside in the dark at room temperature for 72 hr. The excess of periodate was destroyed by the addition of ethylene glycol (5 c.c.), and the solution extracted thrice with chloroform (80 c.c.). The chloroform extracts were evaporated and the residue extracted with acetone, which gave a syrup that was repeatedly extracted with hot light petroleum (b. p. 60—80°). Removal

of the light petroleum and distillation of the syrup gave material (0·096 g., 60%), m. p. 30—31° undepressed on admixture with 2 : 3 : 5-tri-*O*-methylarabonolactone, isolated from the previous oxidation with permanganate.

1 : 4 : 6-*Tri*-O-*methyl*-D-*fructose*.—(*a*) Fructose (60 g.) was condensed with acetone (600 c.c.) in the presence of sulphuric acid (0·3%) (cf. Bell, *loc. cit.*), giving 1 : 2·4 : 5-di-*O*-*iso*propylidene-fructose (67·5 g., 78%), m. p. 118—119°, $[\alpha]_D^{16}$ −147° (*c*, 1·5 in $CHCl_3$). This product (58 g.) was converted into the 3-*O*-toluene-*p*-sulphonyl derivative as described above for the 1-*O*-tosyl derivative. The product (*F*) (68 g., 74%) crystallised from aqueous methanol and then from light petroleum (b. p. 60—80°) had m. p. 97—98°, $[\alpha]_D^{17}$ −161° (*c*, 1·0 in MeOH) (Found : C, 54·3; H, 6·0; S, 7·3. Calc. for $C_{19}H_{26}O_8$ : C, 55·1; H, 6·3; S, 7·8%). The *iso*propylidene residues were removed and the glycoside formed by refluxing it (60 g.) with methanolic hydrogen chloride (1·5%; 500 c.c.). The rotation changed : −70·9° (10 min.); +9·1° (1 hr.); +10·5° (2 hr.). The hydrochloric acid concentration was adjusted to 0·5N, and the glycoside was then completely hydrolysed at 85° during 3 hr. Amorphous 3-O-*toluene*-p-*sulphonyl*-D-*fructose* (*G*) (42 g., 87%), $[\alpha]_D^{18}$ −36·5° (*c*, 1·7 in MeOH), was obtained (Found : C, 46·1; H, 5·6; S, 8·6. $C_{13}H_{18}O_8S$ requires C, 46·7; H, 5·4; S, 9·6%).

This compound (*G*) (10·5 g.) in methanolic hydrogen chloride was set aside at 35° for 17 hr., maximum rotation then being attained ($[\alpha]_D$ +1·7°). The mixture was neutralised with diazomethane, the solvent removed, and the residual syrup extracted with ether. Removal of solvent then gave the *furanoside* as a syrup (8·0 g., 73%), $[\alpha]_D^{19}$ +14° (*c*, 2·0 in MeOH) (Found : S, 8·8. $C_{14}H_{20}O_8S$ requires S, 9·2%).

The glycoside (8 g.), dissolved in the minimum quantity of methanol (10 c.c.), was methylated four times with methyl iodide and silver oxide; *methyl* 1 : 4 : 6-*tri*-O-*methyl*-3-O-*toluene*-p-*sulphonyl*-D-*fructoside*, formed a syrup (6·3 g., 70%), $[\alpha]_D^{18}$ +28° (*c*, 1·5 in MeOH) (Found : OMe, 32·1; S, 8·3. $C_{17}H_{26}O_8S$ requires OMe, 32·8; S, 8·5%). Treatment of this product (6·3 g.) with sodium amalgam as described above for (*C*) gave methyl 1 : 4 : 6-tri-*O*-methyl-D-fructoside (3·7 g., 97%) which after distillation at 100°/0·007 mm. had $[\alpha]_D^{18}$ +47° (*c*, 1·0 in MeOH) (Found : OMe, 47·2. Calc. for $C_{10}H_{20}O_6$ : OMe, 52·8%). The lesser methylated derivatives were removed by dissolving the syrup (3·03 g.) in water (150 c.c.) and extracting with chloroform (5 × 150 c.c.) (Macdonald, *J. Amer. Chem. Soc.*, 1935, **57**, 772). The combined chloroform extracts were dried ($Na_2SO_4$) and evaporated. A straw-coloured syrup (*H*) (2·8 g.), $[\alpha]_D^{17}$ +44° (*c*, 1·0 in MeOH), was obtained (Found : OMe, 51·0%).

Attempts to detect any methyl 1 : 4 : 5-tri-*O*-methylfructopyranoside in syrup (*H*) by graded hydrolysis of a portion with hydrobromic acid (0·04N) at 100° (Ford and Peat, *J.*, 1941, 856) were unsuccessful. Preferential formation of the furanoside from the hydrolysed syrup was also attempted. The hydrolysed syrup (0·1 g.) dissolved in methanolic hydrogen chloride (0·5%) was set aside at 18°; the rotation changed from +19·2° (3 min.) to +38·3° (4·5 hr., constant). Since, under these conditions pyranoside formation is unlikely, extraction of an aqueous solution of this fructoside with chloroform should separate any unchanged 1 : 4 : 5-tri-*O*-methylfructose. No difference in rotation was observed in the extracts, from which it was concluded that the sample was pure 1 : 4 : 6-tri-*O*-methylfructose.

The main bulk of (*H*) (2·42 g.) was hydrolysed with sulphuric acid (150 c.c.; 0·1N) at 95° for 2 hr. After purification with charcoal and Filter Cel there was obtained a syrup (1·82 g., 80%), $n_D^{18}$ 1·4643, $[\alpha]_D^{18}$ +19° (*c*, 1·6 in $CHCl_3$), +30° (*c*, 1·13 in $H_2O$) (Found : C, 47·9; H, 8·1; OMe, 40·9. Calc. for $C_9H_{18}O_6$ : C, 48·6; H, 8·2; OMe, 41·9%). Chromatographic analysis gave a single spot $R_G$ 0·91 in solvent (I) and 0·79 in solvent (II) compared with tetramethylglucose $R_G$ 1·0 as control. Attempts to prepare a crystalline phenylosazone were unsuccessful.

(*b*) Crystalline 2 : 3-*O*-*iso*propylidene-D-fructofuranose (7·7 g.) prepared according to Morgan and Reichstein's method (*loc. cit.*) was subjected to four Purdie methylations; 1 : 4 : 6-*tri*-O-*methyl*-2 : 3-O-iso*propylidenefructose* (*J*) was obtained as a chromatographically pure (naphtharesorcinol spray), mobile syrup (8·2 g., 90%), $[\alpha]_D^{18}$ +10° (*c*, 1·3 in EtOH) (Found : OMe, 35·1. $C_{12}H_{22}O_6$ requires OMe, 35·5%). Removal of the *iso*propylidene group with 0·1N-sulphuric acid gave chromatographically pure 1 : 4 : 6-tri-*O*-methylfructose as a mobile syrup (6·0 g. from 8·0 g.; 89%), $n_D^{18}$ 1·4638, $[\alpha]_D^{19}$ +24° (initial) ⟶ +27° (2·5 hr.) (*c*, 1·2 in $H_2O$).

*Characterisation of* 1 : 4 : 6-*Tri*-O-*methyl*-D-*fructose*.—Syrupy 1 : 4 : 6-tri-*O*-methyl-D-fructose (1·2 g.) synthesised by both methods was oxidised with nitric acid, under the conditions described for 3 : 4 : 6-tri-*O*-methyl-D-fructose, and 4 : 6-di-*O*-methylfructuronic acid (0·5 g.) was obtained as needles, m. p. 107—109°, $[\alpha]_D$ +18·4° (*c*, 0·9 in $H_2O$).

1 : 3 : 4-*Tri*-O-*methyl*-D-*fructose*.—Methyl 1-*O*-toluene-*p*-sulphonyl-D-fructofuranoside (*C*) (30 g.) in pyridine (450 c.c.) mixed with triphenylmethyl chloride (60 g.) was kept at room

temperature for 4 days. After removal of crystalline triphenylmethanol the mixture was poured into ice–water (750 c.c.) with vigorous stirring. *Methyl* 1-O-*toluene*-p-*sulphonyl*-6-O-*trityl*-D-*fructoside* separated as a sticky gum which hardened to an amorphous solid when washed continuously with water for 2 weeks. An ethereal solution of the solid was washed with dilute acetic acid (pH 4) (4 times), saturated sodium hydrogen carbonate solution (3 times), and water (4 times), then dried ($Na_2SO_4$), and the solvent removed, giving an amorphous solid *product* (*K*) (55·2 g., 108%), $[\alpha]_D^{18}$ +7·5° (*c*, 2·40 in MeOH) (Found: S, 4·2. $C_{33}H_{34}O_8S$ requires S, 5·8%).

The amorphous solid (*K*) (28·8 g.) in methanol (260 c.c.) and water (50 c.c.) was treated with sodium amalgam (4%) for 60 hr. at 45° and the solid product (19·1 g., 90%), $[\alpha]_D^{18}$ +12° (*c*, 1·9 in MeOH), isolated as before. Methylation thrice with methyl iodide and silver oxide gave a viscous syrup, $n_D^{18}$ 1·5695 (17·5 g. from 18·9 g., 95%), $[\alpha]_D^{19}$ +9·2° (*c*, 1·1 in MeOH) (Found: OMe, 16·7; trityl, 57·6. Calc. for $C_{29}H_{34}O_6$: OMe, 25·9; trityl, 50·8. Calc. for $C_{29}H_{34}O_6$,$CPh_3$·OH: OMe, 16·8; trityl, 65·8%). All attempts to remove contaminating triphenylmethanol were unsuccessful.

A cooled saturated solution of hydrobromic acid in glacial acetic acid (10 c.c.) was added to crude methyl 1 : 3 : 4-tri-*O*-methyl-6-*O*-trityl-D-fructoside (16 g.) dissolved in glacial acetic acid (30 c.c.) cooled to 0°. After 2 min. the mixture was poured into 0·1N-sulphuric acid (100 c.c.), and the product filtered. The filtrate was heated at 95° for 1 hr. to ensure complete removal of the glycosidic methoxyl group. Extraction with chloroform thrice, and removal of the chloroform, gave 1 : 3 : 4-tri-*O*-methylfructose (4·2 g., 57%) which partly crystallised. The crystals (1·5 g.) after recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) had m. p. 75°, $[\alpha]_D^{20}$ −56·2° (*c*, 1·05 in $H_2O$) (Found: C, 48·65; H, 8·2; OMe, 41·7. Calc. for $C_9H_{18}O_6$: C, 49·1; H, 8·35; OMe, 41·9%). Chromatographic analysis of the mother liquors (2·74 g.) revealed the presence of tetra-*O*-methylfructose contaminating the 1 : 3 : 4-tri-*O*-methylfructose. Separation was effected on silica (Bell and Palmer, *loc. cit.*). The trimethyl sugar was isolated as a pale yellow syrup (1·31 g.) which slowly crystallised; the solid had m. p. 75°.

1 : 4 : 5-*Tri*-O-*methyl*-D-*fructose*.—2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose (36 g.) dissolved in N-sulphuric acid (1000 c.c.) was kept at 25° for 10 hr. and the solution then neutralised by passage through anion-exchange resin (IR-4B). The eluate (reduced to 250 c.c. by evaporation) was then extracted thrice with chloroform (500 c.c.); evaporation of the aqueous solution gave a syrup which on chromatographic analysis showed only the presence of 2 : 3-*O*-*iso*propylidene-fructose and fructose. Attempted separation of these two sugars with boiling acetone–ethyl acetate was reasonably successful, and after removal of the acetone–ethyl acetate the residual syrup was distilled twice at 200°/0·04 mm. The crude 2 : 3-*O*-*iso*propylidene-D-fructopyranose (7 g.) was acetylated with acetic anhydride and anhydrous sodium acetate; 1 : 4 : 5-tri-*O*-acetyl-2 : 3-*O*-*iso*propylidene-D-fructose formed prisms (7·38 g.), m. p. 55—56° (from aqueous ethanol), $[\alpha]_D^{18}$ +18° (*c*, 1·1 in ethanol) (Found: C, 51·8; H, 6·35. Calc. for $C_{15}H_{22}O_9$: C, 52·0; H, 6·4%). The acetyl groups were removed with cold N-sodium hydroxide, and syrupy, chromatographically pure, 2 : 3-*O*-*iso*propylidene-D-fructopyranose (5·1 g.), $[\alpha]_D^{19}$ +29° (*c*, 1·1 in EtOH), was obtained (Wolfrom, Shilling, and Binkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4544, record $[\alpha]_D^{24}$ +28·2° in EtOH, for this compound).

This syrup was methylated five times with methyl iodide and silver oxide and gave after distillation a chromatographically pure syrup (4·51 g., 74%), b. p. 100°/0·09 mm., $n_D^{17}$ 1·4512, $[\alpha]_D^{17}$ +35° (*c*, 1·34 in EtOH). Hydrolysis with sulphuric acid (100 c.c.; 0·1N) at 95° for 2 hr. gave a syrupy *ether* (3·07 g. from 4·4 g., 82%), $n_D^{17}$ 1·4772, $[\alpha]_D^{18}$ −143° (*c*, 1·0 in $H_2O$) (Found: OMe, 41·0. $C_9H_{18}O_6$ requires OMe, 41·9%), $R_G$ 0·76 and 0·61 solvents I and II as eluant, respectively. The crystalline phenylosazone had m. p. 66—67°, alone or on admixture with the phenylosazone obtained from 4 : 5-dimethylfructose.

3 : 4-*Di*-O-*methyl*-D-*fructose*.—(*a*) Methyl 1-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-D-fructoside (*K*) (25 g.) was methylated with methyl iodide and silver oxide thrice and gave a viscous syrupy *ether* (23·7 g., 91%), $n_D^{18}$ 1·5608, $[\alpha]_D$ +14° (*c*, 1·5 in MeOH) (Found: OMe, 14·9. $C_{35}H_{38}O_8S$ requires OMe, 15·1%). The toluene-*p*-sulphonyl group was more resistant to fission with sodium amalgam in methanol than that of methyl 3 : 4 : 6-tri-*O*-methyl-1-*O*-toluene-*p*-sulphonyl-fructoside, and treatment had to be continued for 30 hr. A viscous *product* (14·5 g. from 22·5 g., 86%), $[\alpha]_D$ +24° (*c*, 1·3 in MeOH), was obtained (Found: OMe, 20·1. $C_{28}H_{32}O_6$ requires OMe, 20·0%). The trityl residue was removed as in the previous synthesis, the sugar being left in contact with hydrobromic acid for a longer period (10 min.). The syrup obtained after hydrolysis with sulphuric acid was purified by successive solution in acetone, ethanol, and chloroform, followed by agitation of an ethanolic solution with anion exchange resin (IR-4B) for 2 hr. An

amber-coloured syrup was isolated (4·18 g. from 13·7 g.; 68%) which showed, on chromatographic analysis, the presence of tetra- and tri-*O*-methyl- in addition to di-*O*-methyl-fructose. Separation was effected by elution on powdered cellulose with *n*-butanol–light petroleum (b. p. 100—120°) (3 : 7) as eluant. After the complete removal of the tetra- and tri-*O*-methyl fractions (2·3 g.) the solvent proportions were changed to 1 : 1, and **3** : 4-di-*O*-methylfructose (1·22 g.), $n_D^{18}$ 1·4809, $[\alpha]_D^{14}$ −62° (constant value) (*c*, 3·6 in $H_2O$), was obtained (Found: OMe, 28·0. Calc. for $C_8H_{16}O_6$: OMe, 29·8%), $R_G$ 0·66 and 0·22 in solvents (I) and (II), respectively.

(*b*) **2** : 3-*O*-*iso*Propylidene-**1** : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (*L*) (33·9 g., 23%) was prepared from D-fructose (50 g.) by Morgan and Reichstein's method (*loc. cit.*), the yield being improved by the addition of acetaldehyde (0·1 c.c.) during the condensation with acetone; the compound had m. p. 132—133°, $[\alpha]_D^{16}$ +15·0° (*c*, 1·3 in EtOH) (Found: C, 52·5; H, 5·3; S, 11·7. Calc. for $C_{23}H_{26}O_{10}S_2$: C, 52·3; H, 5·3; S, 11·8%). The *iso*propylidene group was removed and the glycoside formed by treatment with 1% methanolic hydrogen chloride; *methyl* **1** : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructoside* (*M*) was isolated as a non-reducing glass in 85% yield; it had $[\alpha]_D$ +14·7° (*c*, 1·36 in MeOH) (Found: S, 13·3; OMe, 6·1. $C_{21}H_{26}O_{10}S_2$ requires S, 13·6; OMe, 6·6%). The product (*M*) (13·3 g.) was methylated twice with methyl iodide and silver oxide, and *methyl* **3** : 4-*di*-O-*methyl*-**1** : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructoside* (*N*) isolated as a viscous syrup (12·5 g., 90%), $[\alpha]_D^{20}$ +20° (*c*, 1·0 in MeOH) (Found: S, 12·0; OMe, 18·7. $C_{23}H_{30}O_{10}S_2$ requires S, 12·1; OMe, 17·6%). Treatment of (*N*) (12·1 g.) with sodium amalgam as above gave a syrup (3·9 g., 77%) which on chromatographic analysis (acid naphtharesorcinol spray) showed slight contamination with methyl tri-*O*-methylfructoside. Attempted purification by fractional distillation was unsuccessful; the main fraction (2·10 g.) distilled at 150°/0·06 mm. as a pale syrup, $[\alpha]_D^{18}$ +31·6° (*c*, 1·1 in MeOH) (Found: OMe, 43·8. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). This (1·8 g.) was hydrolysed to **3** : 4-di-*O*-methylfructose (1·1 g.) with 0·1N-sulphuric acid and purified from tri-*O*-methylfructoses by separation on powdered cellulose as in the previous synthesis of this derivative. A viscous syrup (1·04 g.) was obtained which had $n_D^{18}$ 1·4817, $[\alpha]_D^{16}$ −19·6° (initial), −35° (17 hr.), −39° (40 hr., const.) (*c*, 1·1 in MeOH), −63° (constant value; *c*, 1·1 in $H_2O$) (Found: OMe, 28·6. Calc. for $C_8H_{16}O_6$: OMe, 29·8%).

*Characterisation of* **3** : 4-*Di*-O-*methyl*-D-*fructose*.—**3** : 4-Di-*O*-methyl-D-fructose (0·74 g.) was oxidised with sodium metaperiodate (40 c.c.) (0·6M) and then with bromine water according to the conditions described by Arni and Percival (*loc. cit.*). Conversion into the methyl ester gave a syrup (0·25 g.) which distilled at 140°/0·03 mm.; the distillate had $n_D^{20}$ 1·4441, $[\alpha]_D^{20}$ −55·1° (*c*, 2·1 in MeOH).

The distilled (−)-dimethoxysuccinate (0·075 g.) on treatment with methanolic ammonia gave (−)-dimethoxysuccinamide (0·05 g.), m. p. 275—276°, $[\alpha]_D^{21}$ −90·3° (*c*, 0·6 in $H_2O$). The corresponding *NN'*-dimethyl-(−)-dimethoxysuccinamide was obtained in good yield; it had m. p. 204—205°, unchanged on admixture with an authentic specimen, $[\alpha]_D^{20}$ −132° (*c*, 0·85 in $H_2O$) (Found: C, 47·1; H, 8·1; N, 13·3. Calc. for $C_8H_{16}O_4N_2$: C, 47·0; H, 7·9; N, 13·7%).

**4** : 5-*Di*-O-*methyl*-D-*fructose*.—**1** : **2**-**4** : 5-Di-*O*-*iso*propylidene-**3**-*O*-toluene-*p*-sulphonyl-D-fructose (*F*) (15·9 g.), dissolved in acetic acid (80%; 80 c.c.), was kept at 60° for 3·5 hr. (Ohle and Just, *loc. cit.*). The acetic acid was removed by distillation and the residue dissolved in ether; the ethereal solution was washed with sodium hydrogen carbonate solution (thrice) and with water, and light petroleum (b. p. 60—80°) added to turbidity. Long needles were deposited of **1** : 2-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-fructose (13 g., 91%), m. p. 124—125°; $[\alpha]_D^{20}$ −112° (*c*, 1·2 in $CHCl_3$), −128° (*c*, 1·2 in MeOH) (Found: C, 51·1; H, 6·1; S, 8·4. Calc. for $C_{16}H_{22}O_8S$: C, 51·3; H, 5·9; S, 8·6%). Methylation thrice with methyl iodide and silver oxide gave a *dimethyl ether* (92%), prisms (from aqueous methanol), m. p. 84—85°, $[\alpha]_D^{17}$ −121° (*c*, 1·0 in MeOH) (Found: C, 53·9; H, 6·4; OMe, 16·5; S, 7·8. $C_{18}H_{26}O_8S$ requires C, 53·7; H, 6·5; OMe, 15·5; S, 8·0%).

The toluene-*p*-sulphonyl group was removed by treatment with 4% sodium amalgam for 48 hr. at 45°. The product, **4** : 5-*di*-O-*methyl*-**1** : 2-*O*-iso*propylidene*-D-*fructose*, after distillation at 130°/0·10 mm. and recrystallisation from light petroleum (b. p. 60—80°) formed hygroscopic needles (4·34 g., 94%), m. p. 64—65°, $[\alpha]_D^{18}$ −169° (*c*, 1·0 in MeOH) (Found: C, 53·2; H, 7·9; OMe, 24·0. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 25·0%).

**4** : 5-Di-*O*-methyl-**1** : 2-*O*-*iso*propylidene-D-fructose (4·0 g.) dissolved in sulphuric acid (0·1N; 100 c.c.) was heated at 95° for 3 hr. Neutralisation by passage through anion-exchange resin (IR-4B) and evaporation gave a syrup (3·27 g., 95%) which crystallised completely. The crystals were dissolved in hot ethanol (2 c.c.) and warm carbon tetrachloride (50 c.c.) was added;

needles of **4** : 5-*di*-O-*methyl*-D-*fructose* were deposited, m. p. 104—105°, $[\alpha]_D^{15}$ −167° (*c*, 1·3 in $H_2O$) (Found: C, 46·2; H, 7·9; OMe, 28·3. $C_8H_{16}O_6$ requires C, 46·15; H, 7·7; OMe, 29·8%). These gave on chromatographic analysis a single spot, $R_G$ 0·49 in solvent (I), 0·14 in solvent (II). The crystalline phenylosazone had m. p. 67—68° (from aqueous ethanol), $[\alpha]_D^{19}$ −27·5° ⟶ −8·2°) (*c*, 1·1 in ethanol). Orange needles of **4** : 5-*dimethylfructose* **2** : 5-*dichlorophenylhydrazone*, m. p. 102°, $[\alpha]_D^{17}$ −45° (*c*, 0·2 in $H_2O$), were obtained on refluxing an alcoholic solution of this dimethyl ether with **2** : 5-dichlorophenylhydrazine (Found: C, 45·0; H, 5·3; N, 7·85. $C_{14}H_{20}O_5N_2Cl_2$ requires C, 45·8; H, 5·4; N, 7·6%).

4-O-*Methyl*-D-*fructose*.—Three methylations with Purdie reagents of **2** : 3-*O*-*iso*propylidene-**1** : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (*L*) (11·4 g.) gave crystalline 4-O-*methyl*-**2** : 3-O-iso*propylidene*-**1** : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructose* (11·6 g., 91%), m. p. 112—113°, $[\alpha]_D^{19}$ +23° (*c*, 1·5 in EtOH) (Found: C, 52·8; H, 5·4; OMe, 5·95. $C_{24}H_{30}O_{10}S_2$ requires C, 53·1; H, 5·6; OMe, 5·7%). Removal of the toluenesulphonyl groups and distillation gave a 4-O-*methyl*-**2** : 3-O-iso*propylidene*-D-*fructose* (4·2 g.), b. p. 150°/0·05 mm., $[\alpha]_D$ +6·5° (*c*, 1·5 in EtOH) (Found: OMe, 13·0. $C_{10}H_{18}O_6$ requires OMe, 13·25%).

Hydrolysis of this syrup (3·48 g.) with sulphuric acid (0·1N; 150 c.c.) at 95° for 3 hr. gave 4-*O*-methylfructose (2·91 g., 100%), $n_D^{18}$ 1·4905, $[\alpha]_D^{18}$ −43° ⟶ −61° (72 hr., const.) (*c*, 1·3 in MeOH), −93° ⟶ −97° (4 days, const.) (*c*, 1·0 in $H_2O$) (McDonald and Jackson, *loc. cit.*, record $[\alpha]_D$ −87·5 in $H_2O$) (Found: OMe, 16·3. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Chromatographic analysis of this syrup showed a single spot, $R_G$ 0·37, in solvent (I). The phenylosazone had m. p. 157—158° (from aqueous acetone), undepressed on admixture with authentic 4-*O*-methylglucosazone, $[\alpha]_D^{17}$ −35° ⟶ −14° (*c*, 0·3 in $H_2O$) (cf. Knauf, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1447, who record m. p. 158—159°, $[\alpha]_D$ −36·0 ⟶ −14·4° for 4-*O*-methylglucosazone).

*Characterisation of* 4-O-*Methyl*-D-*fructose*.—Oxidation of the above syrup (0·50 g.) was carried out as for the **3** : 4-di-*O*-methylfructose. The dimethyl (−)-hydroxymonomethoxysuccinate (0·128 g.) had $n_D^{17}$ 1·4510, $[\alpha]_D^{17}$ −41° (*c*, 1·3 in MeOH). Crystalline D-*threo*-2-hydroxy-3-methoxysuccinamide had m. p. 198—200°. The *bismethylamide* was also obtained and after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave long needles, m. p. 137°, $[\alpha]_D$ −103° (*c*, 0·6 in $H_2O$) (Found: C, 44·2; H, 7·4; N, 13·5. $C_7H_{14}O_4N_2$ requires C, 44·2; H, 7·4; N, 14·7%). These two derivatives have been synthesised from tartaric acid and had melting points and rotation identical with the above.

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## 633. *The Decomposition of Hydrogen Peroxide by Ceric Salts. Part I. The Action of Ceric Sulphate.*

By SHALOM BAER and GABRIEL STEIN.

In the pH range of 0—1·4 the reaction between solutions of ceric sulphate and hydrogen peroxide can be represented by two processes:

(1) $H_2O_2 + Ce^{4+} \longrightarrow HO_2 + H^+ + Ce^{3+}$

(2) $HO_2 + Ce^{4+} \longrightarrow O_2 + H^+ + Ce^{3+}$

without consideration of the actual state of the reacting entities in the solution. It is shown that reoxidation of the $Ce^{3+}$ formed does not occur at all and that the reaction $H_2O_2 + HO_2 \longrightarrow H_2O + O_2 + OH$ does not take place at an appreciable rate; OH radicals are proved to be absent from the system, which thus serves as a source of $HO_2$ radicals alone. Some experiments using ceric perchlorate solutions are described which indicate that the formation of a stable peroxide complex in this case modifies the reaction with hydrogen peroxide.

THE decomposition of hydrogen peroxide by various metal ions and particularly by those of iron has been the subject of many recent investigations (for reviews, see, *e.g.*, Uri, *Chem.*

*Reviews*, 1952, **50**, 375; Baxendale, *Adv. Catalysis*, 1952, **4**, 31; Weiss, *ibid.*, p. 343). Although the detailed mechanism of these processes is not completely elucidated, it seems to be established that a reversible change between the valencies of $Fe^{2+}$ and $Fe^{3+}$, leading to the formation of transient entities such as the radicals OH and $HO_2$ and their dissociation products, plays an important part. It is because of the simultaneous formation of several different transient entities that the exact rôle of each of them is so difficult to elucidate in processes where, as, *e.g.*, in the oxidation of organic substrates with Fenton's reagent, this system is employed.

It therefore seemed useful to propound a system wherein the number of labile intermediates simultaneously existing is a minimum, and the reactions of the remaining ones can be clearly demonstrated. Such might be the case with a metal ion which reacts with hydrogen peroxide to form an ion of lower valency, if the latter ion is itself incapable of decomposing hydrogen peroxide and is not itself reoxidised by any of the labile intermediates occurring in the reaction. If, moreover, the intermediates do not attack hydrogen peroxide, a further simplification of the reaction mechanism can be obtained. It is now shown that the reaction between solutions of ceric sulphate and hydrogen peroxide appears to have these characteristics. This system has been used for the determination of hydrogen peroxide (Hart and Matheson, *Discuss. Faraday Soc.*, 1952, **12**, 169). Treadwell and Hall ("Analytical Chemistry," Wiley, New York, 8th Edn., Vol. II, p. 752) describe this reaction as suitable for the determination of $Ce^{4+}$ if a large excess of hydrogen peroxide is avoided. It will be shown that any such implied deviation from the stoicheiometric ratio is not due to any reaction of cerium ions but to impurities present in the materials normally used.

## Experimental

Experiments were carried out in a vessel of approx. 200 ml. capacity, fitted with mercury-sealed stirrer, gas burette, and burette for the addition of liquids, all *via* ground-glass joints. The temperature of the thermostat containing the vessel was regulated to $\pm 0{\cdot}1°$, the whole of the gas phase being immersed. A 15% solution of sodium chloride was used as the confining liquid in the gas burette. The well-known reactions between hydrogen peroxide and (*a*) excess of ferrous sulphate (no gas evolved) or (*b*) ferric sulphate solution containing traces of ferrous sulphate (oxygen evolved according to: $2H_2O_2 \longrightarrow 2H_2O + O_2$) were used to calibrate the apparatus. Most experiments were carried out at $27° \pm 0{\cdot}1°$. The variables measured were (*a*) amount of oxygen evolved, (*b*) amount of hydrogen peroxide decomposed, and (*c*) amount of ceric ion reduced. Two of these are sufficient to fix all relations, and these were chosen according to the relative concentrations.

$Ce^{4+}$ was determined by addition of excess of ferrous sulphate, freshly standardised against potassium dichromate, which was used also for determination of the excess. No interaction with $Ce^{3+}$ was observed. Diphenylamine was used as indicator. Hydrogen peroxide was determined (i) by potassium permanganate solution standardised against arsenious oxide ($Ce^{3+}$ did not interfere in the cold), or (ii) by adding it to excess of ferrous sulphate, the excess being determined by dichromate with diphenylamine as indicator.

The water used in preparing all solutions was triply distilled (redistillations from alkaline permanganate and dilute phosphoric acid). Ordinary distilled water leads to faulty results.

Ceric sulphate solutions were prepared from "AnalaR" ceric ammonium nitrate *via* the hydroxide, precipitated by ammonia (Baker's "Analysed"). The precipitate was washed several times with triply distilled water, and dissolved in dilute sulphuric acid ("AnalaR"). Ceric perchlorate solutions were prepared similarly, "AnalaR" perchloric acid being used in the last step. In certain experiments ceric sulphate and ceric perchlorate solutions were prepared from ceric oxide (spectroscopically pure; Messrs. Johnson, Matthey and Co.). The hydrogen peroxide and the iron salts were of "AnalaR" quality.

## Results and Discussion

Experiments with ceric sulphate solutions in excess, to which hydrogen peroxide solutions were added, at various pH values, are recorded in Table 1. An instantaneous reaction occurs which leads to the complete decomposition of the peroxide, unlike the decomposition of hydrogen peroxide by ferric sulphate which is slow, as is to be expected

from the respective reduction potentials. It will be seen from Table 1 that the quantitative results agree exactly with a mechanism according to which the relative quantities of oxygen evolved, hydrogen peroxide decomposed, and ceric ion reduced are

TABLE 1. *Reaction between excess of ceric sulphate solutions (from " AnalaR " material) and added hydrogen peroxide.*

| $Ce^{4+}$ solution : $10^{-2}$N | quantity, $10^{-4}$ equiv. | $H_2O_2$ solution : $10^{-2}$N | quantity, $10^{-5}$ equiv. | pH | $O_2$ evolved, $10^{-4}$ mole | $Ce^{4+}$ reduced, $10^{-5}$ equiv. |
|---|---|---|---|---|---|---|
| 5·00 | 10·00 | 5·10 | 25·4 | 0·75 | 1·27 | — |
| 5·00 | 10·00 | 5·10 | 25·4 | 0·75 | 1·28 | — |
| 0·86 | 3·44 | 1·67 | 3·19 | 0·5 | — | 3·18 |
| 1·04 | 4·16 | 2·02 | 3·01 | 0·1 | — | 3·01 |
| 1·04 | 4·16 | 2·02 | 3·02 | 0·1 | — | 3·04 |
| 1·00 | 6·00 | 8·04 | 4·02 | 0·1 | — | 4·02 |

related by the sum of the two reactions (1) and (2) (p. 3176). Within the experimental error it is shown, that $Ce^{3+}$ ions are not reoxidised under these conditions and also that other processes involving an attack on hydrogen peroxides are absent. However, such processes are not favoured by the conditions employed for the work reported in Table 1. The use of high concentrations of hydrogen peroxide in excess, to which ceric sulphate solutions are added, would favour the occurrence of processes such as

$$(3)\ H_2O_2 + HO_2 \longrightarrow H_2O + O_2 + OH$$

leading to the formation of other radicals and the consequent decomposition of hydrogen peroxide in quantities not in agreement with the above simple scheme. Under these conditions, and with " AnalaR "-quality ceric sulphate, the results shown in Tables 2*a* and 2*b* were obtained, and it appears that additional reactions are occurring.

TABLE 2*a*. *Reaction between excess of hydrogen peroxide solution* (40 *ml.*) *and ceric sulphate solution (from* " AnalaR " *material).*

| No. | $H_2O_2$, N | pH | $Ce(SO_4)_2$ solution : normality, $10^{-1}$N | ml. | $Ce^{4+}$ reduced, $10^{-4}$ mole | $O_2$ evolved, $10^{-4}$ mole |
|---|---|---|---|---|---|---|
| 1 | 1·92 | 1·4 | 1·00 | 4·00 | 4·00 | 2·21 |
| 2 | 1·91 | 1·35 | 1·04 | 4·07 | 4·28 | 2·39 |
| 3 | 1·96 | 1·3 | 1·00 | 4·00 | 4·00 | 2·23 |
| 4 | 1·87 | 1·1 | 1·00 | 4·00 | 4·00 | 2·18 |
| 5 | 1·76 | 1·1 | 1·00 | 4·00 | 4·00 | 2·17 |

TABLE 2*b*. *Showing rate of production of oxygen in experiments of Table* 2*a.*

| Time, min., after addition of $Ce^{4+}$ | Gas burette reading, ml., in Expt. 1 | 2 | 3 | 4 | 5 | Time, min., after addition of $Ce^{4+}$ | Gas burette reading, ml., in Expt. 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 11·00 | 11·45 | 10·95 | 11·10 | 11·35 | 15 | 11·25 | 11·70 | 11·40 | 11·40 | 11·65 |
| 10 | 11·15 | 11·65 | 11·25 | 11·35 | 11·55 | 20 | — | 11·73 | 11·50 | — | — |

However, on repeating these experiments with ceric sulphate solutions prepared from spectroscopically pure material, it was shown (Tables 3*a* and 3*b*) that there were no reactions in addition to those required by (1) and (2) even in the presence of high concentrations of hydrogen peroxide. The results with the less pure salt are presumably due to traces of impurities which decompose the peroxide catalytically, a process apparently not initiated by pure cerium salts under these conditions.

It appears therefore that $HO_2$ radicals, if they are in fact formed as postulated in this reaction mechanism, are incapable of reoxidising cerous ions. This is in agreement with the known thermodynamic data (Uri, *loc. cit.*). It appears also that under these conditions $HO_2$ radicals do not attack hydrogen peroxide molecules. This confirms previous indirect postulates (Uri, *loc. cit.*; Ebert and Boag, *Discuss. Faraday Soc.*, 1952, **12**, 189), and indicates that, when such attack does occur, it is the anion related to the radical, namely $O_2^-$, which is responsible for it. Under the conditions employed, the $HO_2$ radical will be only inappreciably dissociated ($K_{HO_2} \sim 10^{-12}$).

In using ceric sulphate solutions there is no evidence that the $HO_2$ radicals do not

appear as such in the course of the reaction, but remain implicit in a complex; such evidence seems to appear when ceric perchlorate solutions are used to decompose hydrogen peroxide. In spite of the fact that the oxidation–reduction potential of these solutions is

TABLE 3*a*. *Reaction between excess of hydrogen peroxide solution* (40 *ml.*) *and ceric sulphate solution* (*from spectroscopically pure material*).

| No. | $H_2O_2$, N | pH | $6{\cdot}4 \times 10^{-2}$N-$Ce(SO_4)_2$ solution ml. | $Ce^{4+}$ reduced, $10^{-4}$ mole | $O_2$ evolved, $10^{-4}$ mole |
|---|---|---|---|---|---|
| 1 | 0·50 | 1·4 | 4·5 | 2·88 | 1·40 |
| 2 | 1·00 | 1·3 | 4·5 | 2·88 | 1·43 |
| 3 | 2·00 | 1·3 | 4·5 | 2·88 | 1·43 |
| 4 | 5·00 | 1·2 | 4·5 | 2·88 | 1·43 |

TABLE 3*b*. *Showing rate of production of oxygen in experiments in Table* 3*a*.

| Time, min. after addition of $Ce^{4+}$ | Gas burette reading, ml., in Expt. 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 10 | 9·20 | 9·32 | 9·30 | 9·33 |
| 20 | 9·20 | 9·30 | 9·30 | 9·30 |

higher than in the case of the sulphate solutions, no instantaneous decomposition of the peroxide takes place, but a deep red complex is formed, yielding a precipitate under suitable conditions even in strongly acid solutions. The slow evolution of oxygen from the solution is a function of the pH.

Experiments are now in progress to determine the composition of the complex and the kinetics of its decomposition. Although in solutions containing sulphate the ceric ion is mainly present as the complex $Ce(SO_4)_3^{2-}$ under the conditions employed (Hardwick and Robertson, *Canadian J. Chem.*, 1951, **29**, 828), yet it appears that in perchlorate solutions such as we used, the complex with perchlorate anion plays only a very minor rôle, and the ions mainly present are $Ce^{4+}$ and $Ce(OH)^{3+}$. The complex with hydrogen peroxide obtained here is clearly related to that discussed by Evans, George, and Uri (*Trans. Faraday Soc.*, 1949, **45**, 230) for ferric perchlorate solutions, which they identify as $Fe(HO_2)^{2+}$. However, at least in the case of ceric ions, preliminary results indicate that in the formation of the complex two ceric ions are involved per molecule of peroxide complex.

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## 634. *The Use of Radioactive Sulphur* [$^{35}$S] *in a Study of the Oxidation of* cyclo*Hexyl Methyl Sulphide with* tert.*-Butyl Hydroperoxide.*

By G. AYREY, D. BARNARD, and C. G. MOORE.

*cyclo*Hexyl methyl [$^{35}$S]sulphoxide has been synthesised from methane-[$^{35}$S]thiol and has been used to show the irreversibility of the primary oxidation step in the conversion of *cyclo*hexyl methyl sulphide into the corresponding sulphoxide by *tert.*-butyl hydroperoxide.

OVER a wide range of experimental conditions the oxidation of *cyclo*hexyl methyl sulphide to *cyclo*hexyl methyl sulphoxide by *tert.*-butyl hydroperoxide in benzene is stoicheiometrically represented by the equation :

$$C_6H_{11}\cdot SMe + Bu^tO\cdot OH = C_6H_{11}\cdot SO\cdot Me + Bu^tOH$$

In a kinetic study of this oxidation made by Dr. K. R. Hargrave in these laboratories (unpublished work) a strong, auto-retardative effect due to the sulphoxide has been observed. It is a reasonable assumption that, whatever the detailed reaction mechanism, the formation of sulphoxide from sulphide occurs in one individual step, although for the present purpose the mechanism of this oxygen transfer is of no consequence. The reversibility of this oxidation step is one possibility which would account for the observed retardation and the present work was undertaken to verify or disprove this.

The principle of the investigation can be stated as follows. A relatively large excess of *cyclo*hexyl methyl sulphide is caused to react with *tert.*-butyl hydroperoxide in benzene

in the presence of sulphoxide labelled with $^{35}S$, under conditions which allow of the major utilisation of the hydroperoxide. The residual sulphide is then rigorously separated from sulphoxide and its activity determined. The absence of activity in this sulphide will demonstrate the irreversibility of the primary oxidation process.

*cyclo*Hexyl methyl [$^{35}S$]sulphide was prepared from methane[$^{35}S$]thiol and *cyclo*hexene and oxidised, without isolation, to *cyclo*hexyl methyl [$^{35}S$]sulphoxide with *tert.*-butyl hydroperoxide. The overall yield indicated by a trial synthesis was 83%. Purification was achieved by fractional distillation, and traces of *cyclo*hexyl methyl [$^{35}S$]sulphide were finally removed by a chromatographic procedure.

The necessarily rigorous separation of sulphide from sulphoxide after oxidations carried out in the presence of labelled sulphoxide was best achieved by fractional elution from alumina. The results of control experiments in which *tert.*-butyl hydroperoxide was replaced by *tert.*-butanol, and of actual oxidation runs, are given below, the activities of the isolated samples of sulphide being expressed as the counts per minute of an " infinitely thick " layer of *cyclo*hexyl methyl sulphone assayed under standard conditions. This final counting form was superior, for low-activity samples, to the standard " infinitely thick " precipitates of benzidine sulphate, chiefly because of increased sensitivity. We have used the latter method for samples of higher activity and have found that, by suitable

TABLE 1. *Activities of products assayed as* cyclo*hexyl methyl sulphone.*

| Compound | Activity (counts/min.) | Activity due to possible reversibility of oxidation step (counts/min.) | % of maximum activity * |
|---|---|---|---|
| *cyclo*Hexyl methyl [$^{35}S$]sulphoxide ... | 261,000 | — | — |
| *cyclo*Hexyl methyl sulphide from : | | | |
| (i) Control A ..... | 29 } Mean 27 | — | — |
| (ii) Control B ..... | 25 } | — | — |
| (iii) Oxidation A ..... | 57 | 30 | 0·064 |
| (iv) Oxidation B ..... | 60 | 33 | 0·071 |

* If equilibration of sulphide and [$^{35}S$]sulphoxide were complete, activities of sulphides from oxidations A and B would be 46,860 counts/min. and 46,590 counts/min. respectively.

refinement of techniques, errors due to non-uniformity of the precipitate and geometry of presentation to the counter can be reduced. With a negligibly small counting error the reproducibility amongst replicates has a standard deviation of about 1%.

The difference in activity between sulphide samples isolated from control and oxidation experiments is thus so slight that it can be concluded that the oxidation step involving oxygen transfer to the sulphide is irreversible under the conditions studied and, moreover, that there is no entity produced during the reaction which is capable of reducing sulphoxide to sulphide.

## EXPERIMENTAL

*Preparation of Inactive Materials.*—*cyclo*Hexyl methyl sulphide was prepared by ultraviolet irradiation of a mixture of methanethiol and *cyclo*hexene (Barnard, Fabian, and Koch, *J.*, 1949, 2442). The pure sulphide (yield 84%) had b. p. 62·2—62·6°/13 mm., $n_D^{20}$ 1·4945 (Found: C, 64·4; H, 10·75; S, 24·6. Calc. for $C_7H_{14}S$: C, 64·6; H, 10·8; S, 24·6%). *cyclo*Hexyl methyl sulphoxide, prepared by Barnard and Hargrave's method (*Analyt. Chim. Acta*, 1951, **5**, 536), had b. p. 88·3°/0·05 mm., $n_D^{22}$ 1·5119 (yield 77%) (Found: C, 57·5; H, 9·75; S, 22·1. Calc. for $C_7H_{14}OS$: C, 57·5; H, 9·65; S, 21·9%). Analysis of the sulphoxide by Barnard and Hargrave's method (*loc. cit.*) indicated a purity of 99·0%. Commercial *tert.*-butyl hydroperoxide was purified by Barnard and Hargrave's method (*ibid.*, p. 476), to give a material, b. p. 28·8°/10 mm., assaying as 99·7% pure.

*Assay of Samples for* $^{35}S$.—(i) The activities of " infinitely thick " samples were determined with a G.E.C. mica end-window Geiger–Müller counter (Type E.H.M.2S). With the high-activity samples sufficient counts were taken to give a standard error of less than ±1%. With the low-activity samples having activities of <60 counts/min. sufficient counts were taken to give a standard error of less than ±2·5%. All count-rates recorded have been corrected for the resolving time of the counter, background (<10 counts/min.), variations in counter efficiency, decay, and sample dilution.

(ii) *Assay as benzidine sulphate.* Samples were oxidised to sulphate ion by the standard

micro-combustion technique and, after suitable dilution with inactive potassium sulphate to give an " infinitely thick " sample, were precipitated as benzidine sulphate according to the method of Henriques, Kistiakowsky, Margnetti, and Schneider (*Ind. Eng. Chem., Anal.*, 1946, **18**, 349). The resulting samples (diam. 2·3 cm.), on a Whatman No. 2 filter, were placed on a duralumin support and adjusted by means of a levelling device to obtain a constant height between sample surface and counter window. This adjustment was previously found to be an important factor in obtaining reproducible count-rates with samples of a given thickness. To minimise the effects of non-uniformity at the edge of the precipitate samples were covered with a mask having an aperture of diam. 1·8 cm. Results (Table 2) of the assay of representative samples indicate the order of reproducibility attained.

TABLE 2. *Assay of* [$^{35}$S] *as benzidine sulphate.*

| Volume of 0·0497M-$K_2SO_4$ (~20 $\mu$c/l. $^{35}$S) (ml.) | Mean sample thickness (mg./cm.$^2$) | Corrected count rate (counts/min.) | Mean corr. count rate (counts/min.) |
|---|---|---|---|
| 8·0 | 27·2 | 2415 | 2426 ± 9 * |
| " | | 2419 | |
| " | | 2443 | |
| 10·0 | 33·7 | 2403 | 2428 ± 6 * |
| " | | 2444 | |
| " | | 2433 | |
| " | | 2441 | |
| " | | 2422 | |
| " | | 2427 | |
| 13·0 | 43·8 | 2406 | 2429 ± 17 * |
| " | | 2418 | |
| " | | 2463 | |

* Error given as standard error of the mean.

(iii) *Assay as liquid* cyclo*hexyl methyl sulphone.* Samples were counted in a polished duralumin cup, of internal diam. 2·52 cm. and depth 0·75 cm., which was covered with a mask having an aperture of diam. 1·8 cm. The physical characteristics of the sulphone were suitable for obtaining samples of reproducible geometry; the liquid flows easily, does not creep, and is non-hygroscopic and involatile. Table 3 records the count-rates for different weights of sul-

TABLE 3. *Assay of* [$^{35}$S] *as* cyclo*hexyl methyl sulphone.*

| Wt. (g.) | 0·3580 | 0·4245 | 0·5112 | 0·5995 | 0·6860 | 0·8061 |
|---|---|---|---|---|---|---|
| Sample thickness (mg./cm.$^2$) | 71·7 | 85·1 | 102 | 120 | 138 | 162 |
| Corr. count rate (counts/min.) | 703 | 693 | 706 | 704 | 716 | 733 |

phone assayed under an accurately reproducible geometry, except for variation in height between sulphone surface and counter-window. The results show that all the sample weights used lie within the " infinite thickness " range and that variation in the sulphone weight from *ca.* 0·36 to 0·80 g. causes <5% increase in the count rate. Activities of [$^{35}$S]sulphone samples obtained in the experiments to be described below were obtained on samples of weight *ca.* 0·52—0·53 g. within which range there will obviously be negligible variation in count rate for any given sample.

*Synthesis of* cyclo*Hexyl Methyl* [$^{35}$S]*Sulphoxide.*—The apparatus used is shown in Fig. 1. Methane[$^{35}$S]thiol (1·15 g., ~12·0 mc) was supplied by The Radiochemical Centre, Amersham. *cyclo*Hexene (3·934 g., 100% excess; freshly chromatographed on alumina under nitrogen) and " AnalaR " acetone (0·10 ml.) contained in the tube *A* were degassed on the vacuum-manifold and then transferred *in vacuo* to the 50-ml. flask *B*. $T_1$ was closed and, with *B* cooled in liquid air, the seal at *C* was broken and the methane[$^{35}$S]thiol distilled *in vacuo* from *D* into the flask *B* which was then sealed off at the constriction *E*. Tube *D* was cooled in liquid air and sealed off at the constriction *F*. The reactants in *B* were irradiated with ultra-violet light, with water-cooling, for 16·0 hr. *B* was re-attached to the vacuum-manifold at *G* and then, with *B* cooled in liquid air, the seal at *H* was broken and a mixture of previously degassed *tert.*-butyl hydroperoxide (2·300 g., 6% excess based on 100% yield of sulphide) and redistilled absolute methanol (25·0 ml.) was distilled *in vacuo* into *B*, and the apparatus sealed off at the constriction *I*. The reactants were heated at 50·0° ± 0·1° for 64 hr. after which time the apparatus was re-attached to the vacuum-manifold at *J* in conjunction with a tube with a seal-off constriction. After evacuation of the apparatus, the latter tube was cooled in liquid air, the seal at *K* broken and about 10 ml. of low-boiling material were distilled *in vacuo* from *B* into the tube which was then

sealed off. This was done to trap any unchanged [$^{35}$S]thiol before opening of *B* to the air. The main apparatus was sealed off at the constriction *L* until required. The flask *B* was broken at *M*, and the contents were transferred to a Vigreux distillation unit (150-ml., a pear-shaped flask). *B* was washed out with successive portions of inactive *cyclo*hexyl methyl sulphoxide (total, 40·1 g.), followed by a little methanol, the total washings being transferred to the distillation unit. After removal of the low-boiling material, the *cyclo*hexyl methyl [$^{35}$S]sulphoxide was distilled *in vacuo* ($10^{-3}$ mm.), to give (i) a small forerun (7·0 g.) and (ii) the main fraction (35·4 g.) (Found: S, 22·0. Calc. for $C_7H_{14}OS$: S, 21·9%). The latter fraction had an activity as sulphone of 265,400 counts/min. and as benzidine sulphate of 181,700 counts/min.

The same synthesis with inactive materials gave an 83% yield of *cyclo*hexyl methyl sulphoxide, b. p. 65°/0·01 mm., $n_D^{20}$ 1·5122. The oxidation of *cyclo*hexyl methyl sulphide to the corresponding sulphoxide was shown to be 96·1% complete after 24·0 hr. at 50°.

*Oxidation of* cyclo*Hexyl Methyl Sulphide to* cyclo*Hexyl Methyl Sulphone.*—The sulphide (1·00 g.) in "AnalaR" benzene (2·0 ml.), light petroleum (b. p. <40°; 2·0 ml.), and "AnalaR" acetic acid (20 ml.) was oxidised with hydrogen peroxide (2·73 ml., assayed as 8·45 mole/l.). The temperature rose to about 40° and was then slowly raised to refluxing temperature (bath at 130°) and held there for 3·0 hr. After removal of the solvents and excess of peracetic acid

FIG. 1.

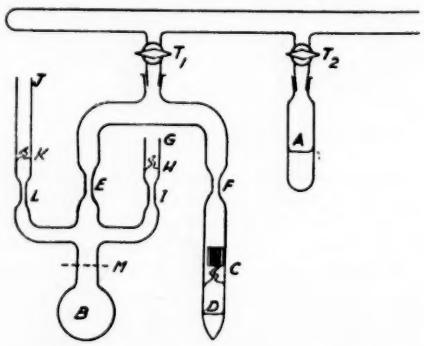
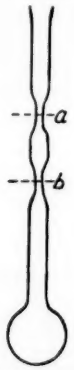



FIG. 2.




the residue was distilled in a small molecular-still, to give the pure sulphone, $n_D^{20}$ 1·4918 (1·07 g., 86%) (Found: C, 51·45; H, 8·8; S, 19·75. Calc. for $C_7H_{14}O_2S$: C, 51·8; H, 8·7; S, 19·7%).

*Chromatographic Separation of* cyclo*Hexyl Methyl Sulphide and* cyclo*Hexyl Methyl* [$^{35}$S]-*Sulphoxide.*—A mixture of inactive sulphide (1·128 g.) and [$^{35}$S]sulphoxide (0·5079 g.), in "AnalaR" benzene (1·0 ml.) and light petroleum (25 ml.; b. p. <40°), was chromatographed on alumina (20 g.; 15 × 1·3 cm.). Successive fractions were eluted with (i) light petroleum (50 ml.), (ii) light petroleum (50 ml.), and (iii) chloroform (125 ml.). The sulphide obtained from the first eluate by removal of most of the petroleum through a gauze-packed column was oxidised to the sulphone (1·22 g., 86·7%) having an activity of 706 counts/min.

The [$^{35}$S]sulphoxide, recovered from eluate (iii) by removal of the solvent, was mixed with more inactive sulphide (1·13 g.), and the mixture rechromatographed as above. The sulphide now obtained from the first eluate gave a sulphone having an activity of 25 counts/min. The low activity of the latter sulphone sample indicates the effectiveness of the separatory method, whilst the comparatively high activity of the first sulphone sample suggests the presence of some *cyclo*hexyl methyl [$^{35}$S]sulphide as impurity in the original [$^{35}$S]sulphoxide. The assay results indicate a maximum percentage of [$^{35}$S]sulphide impurity of 0·05%. This maximum value assumes that the chromatographic procedure is 100% efficient and that in the synthesis of the [$^{35}$S]sulphoxide yields are theoretical.

*Purification of* cyclo*Hexyl Methyl* [$^{35}$S]*Sulphoxide.*—A mixture of the impure [$^{35}$S]sulphoxide (6·73 g.) and inactive sulphide (3·0 ml.) in light petroleum (b. p. <40°, 80 ml.) and benzene (5 ml.) was separated on alumina (120 g.; 31 × 2·3 cm.). The sulphide was eluted with light petroleum (75 ml.). More inactive sulphide (3·0 ml.) in light petroleum (5 ml.) was added to the column and eluted with light petroleum (145 ml.). The [$^{35}$S]sulphoxide was eluted with chloroform (450 ml.) until no further activity could be detected in the eluate. Removal of the solvent and molecular-distillation of the residue from a horizontal pot-still (bath-temp. 45°)

gave pure *cyclo*hexyl methyl [$^{35}$S]sulphoxide (5·6 g.) (Found: S, 22·0. Calc. for $C_7H_{14}OS$: S, 21·9%), having an activity as sulphone of 261,000 counts/min. and as benzidine sulphate of 175,600 counts/min.

Chromatographic separation of inactive sulphide (1·1448 g.) and the purified [$^{35}$S]sulphoxide (0·5274 g.) as described above gave a sulphide fraction having an activity, as sulphone (1·14 g.) (Found: S, 19·6%), of 18 counts/min. This result confirms (i) that the [$^{35}$S]sulphoxide has been purified from the [$^{35}$S]sulphide impurity and (ii) that the chromatographic method is suitable for the rigid separation of sulphide–sulphoxide mixtures.

*Oxidation of* cyclo*Hexyl Methyl Sulphide with* tert.*-Butyl Hydroperoxide in the Presence of* cyclo*Hexyl Methyl Sulphoxide.*—(1) *Trial oxidations.* These experiments were done to determine the conditions favouring a maximum of any possible reversible reaction, and to test the stoicheiometry of the oxidation over an extensive reaction range. Sulphide (3·4383 g., 0·02645 mole), sulphoxide (0·8388 g., 0·00575 mole), and *tert.*-butyl hydroperoxide (0·4997 g., 0·00555 mole) were well mixed in previously degassed benzene (25·0 ml.) and then immediately pipetted into tubes (4 at 6·0 ml. and 1 at 3·0 ml.), degassed, sealed *in vacuo*, and heated at 50·0° ± 0·1° for the appropriate times. The product was analysed for sulphoxide and hydroperoxide by Barnard and Hargrave's method (*Analyt. Chim. Acta*, 1952, **6**, 23). The results (Table 4) confirm that the equation is obeyed up to 85·6% reaction.

TABLE 4. *Reaction of* cyclo*hexyl methyl sulphide with* tert.*-butyl hydroperoxide in the presence of* cyclo*hexyl methyl sulphoxide at* 50·0° ± 0·1°.

| Time (hr.) | 0 | 6·0 | 26·0 | 43·5 | 97·5 |
|---|---|---|---|---|---|
| Sulphoxide (mole) | 0·00585 | — | 0·00856 | 0·00934 | 0·0104 |
| Hydroperoxide (mole) | 0·00546 | 0·00447 | 0·00245 | 0·00156 | 0·00075 |

(2) *Control experiments.* To a mixture of purified *cyclo*hexyl methyl [$^{35}$S]sulphoxide (0·4942 g.) and inactive *cyclo*hexyl methyl sulphide (1·3141 g.) contained in the apparatus shown in Fig. 2 was added, by distillation *in vacuo*, a mixture of previously degassed "AnalaR" benzene (10·0 ml.) and *tert.*-butanol (0·1648 g.), the latter replacing the hydroperoxide of the actual oxidation experiments. The flask was sealed *in vacuo* at the constriction (*a*), and the contents were heated at 50·0° ± 0·1° for 96·0 hr. After freezing in liquid air, the flask was opened and stannous chloride solution (25 ml.; 0·112N) was cautiously added. The flask was sealed at the constriction (*b*), then warmed to room temperature, and the contents were shaken occasionally for 1 hr. The flask was opened and the benzene layer, contained in the narrow neck of the flask, carefully pipetted into a second tube where, together with benzene washings (2 × 5 ml.) from the aqueous phase, it was shaken with potassium dichromate solution (3·0 ml.; 0·05N) to remove the last traces of stannous chloride solution. The benzene layer, together with benzene washings (15 ml.), was pipetted into a third tube, washed with water (8 ml.), and dried by passage through a filter pad of anhydrous magnesium sulphate. The latter was extracted with benzene washings (3 × 5 ml.) of the water phase, followed by pure benzene (5 ml.). After removal of the benzene through a spiral gauze column the product was fractionally eluted from alumina (20 g.) as previously described, to give a sulphide fraction having an activity, as sulphone (1·24 g.), of 29 counts/min. In a duplicate control experiment the sulphide fraction had an activity, as sulphone, of 25 counts/min. These results show (i) the absence of thermal exchange between sulphoxide and sulphide at 50° under the given experimental conditions, and (ii) that the stannous chloride [used to reduce unchanged hydroperoxide in experiment (3)] does not reduce [$^{35}$S]sulphoxide to [$^{35}$S]sulphide to any significant extent.

(3) *Oxidations in the presence of* cyclo*hexyl methyl* [$^{35}$S]*sulphoxide.* The purified [$^{35}$S]sulphoxide (0·3382 g.), inactive sulphide (1·3771 g.), and hydroperoxide (0·1998 g.) in benzene (10·0 ml.) were heated at 50·0° ± 0·1° for 96·0 hr. under conditions identical with those of the trial oxidations and control experiments. Similar working up gave a sulphide fraction which had an activity, as sulphone (0·90 g.), of 57 counts/min.

In a second experiment, with [$^{35}$S]sulphoxide (0·3361 g.), sulphide (1·3775 g.), and hydroperoxide (0·1997 g.), there was obtained a sulphide fraction which had an activity, as sulphone, of 60 counts/min.

We thank Dr. K. R. Hargrave for his interest in this work which forms part of the programme of research undertaken by the Board of the British Rubber Producers' Research Association.

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## 635. *The Mannans of Ivory Nut* (Phytelephas macrocarpa). *Part I. The Methylation of Mannan A and Mannan B.*

By G. O. Aspinall, E. L. Hirst, (the late) E. G. V. Percival, and I. R. Williamson.

Mannans A and B from ivory nut (*Phytelephas macrocarpa*) gave on hydrolysis D-mannose (97·6%), D-galactose (1·8%), and D-glucose (0·8%), and D-mannose (98·3%), D-galactose (1·1%), and D-glucose (0·8%), respectively. Hydrolysis of methylated mannan A gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose (7·3%), 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (1·7%), 2 : 3 : 6-tri-*O*-methyl-D-mannose (83·0%), 2 : 3 : 4-tri-*O*-methyl-D-mannose (6·8%), and a di-*O*-methyl-D-mannose (1·2%). Hydrolysis of methylated mannan B gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose (1·3%), 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (1·3%), 2 : 3 : 6-tri-*O*-methyl-D-mannose (81·8%), 2 : 3 : 4-tri-*O*-methyl-D-mannose (14·3%), and a di-*O*-methyl-D-mannose (1·3%). 2 : 3 : 4-Tri-*O*-methyl-D-mannose was isolated from both hydrolysates as the non-reducing disaccharide 2 : 3 : 4-tri-*O*-methyl-D-mannopyranosyl 2 : 3 : 4-tri-*O*-methyl-D-mannopyranoside. It is concluded that mannan A and mannan B both contain at least two types of molecule, one terminated by a D-mannopyranose residue and the other terminated by a D-galactopyranose residue. The majority of the mannopyranose residues are linked through positions 1 and 4 but 1 : 6-linkages are also present. Mannans A and B differ only in molecular size having average chain lengths of 10—13 and 39—40, respectively.

The chemistry of the endosperm of ivory nut (*Phytelephas macrocarpa*) was first studied by Reiss (*Ber.*, 1889, **22**, 609) who obtained on hydrolysis a sugar that was subsequently identified as mannose by Fischer and Hirschberger (*Ber.*, 1889, **22**, 1155). Several investigators (Johnson, *J. Amer. Chem. Soc.*, 1896, **18**, 214; Baker and Pope, *J.*, 1900, **77**, 676; Ivanov, *Journ. f. Landw.*, 1908, **56**, 217; Pringsheim and Seifert, *Z. physiol. Chem.*, 1922, **123**, 205) studied the polysaccharide extracted from ivory nuts with alkali and showed that it yielded mainly mannose on hydrolysis. Patterson (*J.*, 1923, 1139) methylated the polysaccharide and from the hydrolysate isolated a syrupy trimethylmannose which could be quantitatively converted into crystalline methyl tetra-*O*-methyl-α-D-mannoside. Patterson concluded, therefore, that all the mannose residues were of the ordinary stable type.

Further investigations by Lüdtke (*Annalen*, 1927, **456**, 201) showed that two different mannans could be obtained from delignified ivory nuts by dissolution in cuprammonium solution followed by fractional precipitation with sodium hydroxide. The mannan mixture was separated into two fractions, mannan A (soluble in aqueous sodium hydroxide) and mannan B (insoluble in aqueous sodium hydroxide).

Methylation studies of mannans A and B were carried out by Klages (*Annalen*, 1934, **509**, 159; **512**, 185) who concluded that mannan A consisted of a chain of 80 1 : 4-linked β-D-mannopyranose residues and postulated that mannan B was similarly constituted. More recent investigations by Ward (M.Sc. Thesis, Manchester, 1947) indicated that mannan A had a repeating unit of 15 and that the 1 : 4-linkage was not the only linkage present. The present investigation was undertaken to determine whether the two mannans were similarly constituted and with the aid of modern chromatographic techniques to determine the fine structure of each.

Mannan A was extracted from delignified ivory nut shavings with cold aqueous potassium hydroxide and purified by two precipitations, as the copper complex, with Fehling's solution. Hydrolysis of the mannan, $[\alpha]_D^{15}$ −46° (*c*, 0·7 in N-NaOH), gave D-mannose (97·6%), D-galactose (1·8%), and D-glucose (0·8%), estimated by quantitative paper chromatography (Hirst and Jones, *J.*, 1949, 1659; Duff and Eastwood, *Nature*, 1950, **156**, 848).

The mannan was methylated under nitrogen with sodium hydroxide and methyl sulphate, and subsequently with methyl iodide and silver oxide, to give a product (OMe,

43·5%), which was fractionated by dissolution in chloroform–light petroleum. The methylated mannan A {$[\alpha]_D^{17}$ −22·5° (*c*, 1·0 in $CHCl_3$), OMe, 44·3%)} was hydrolysed successively with anhydrous formic acid and dilute sulphuric acid (Jones, *J.*, 1950, 3292), and the mixture of sugars separated on cellulose. The following fractions were obtained: (1) tetra-*O*-methylmannose (7·3%); (2) tetra-*O*-methylgalactose (1·7%); (3) 2 : 3 : 6-tri-*O*-methylmannose (83·0%); and (4) a mixture of a trimethylmannose and a dimethylmannose. 2 : 3 : 4 : 6-Tetra-*O*-methyl-D-mannose was identified as its aniline derivative, and as the phenylhydrazide of the corresponding 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannonic acid. 2 : 3 : 4 : 6-Tetra-*O*-methyl-D-galactose was identified as its aniline derivative. 2 : 3 : 6-Tri-*O*-methyl-D-mannose was identified as its aniline derivative and as the γ-lactone and phenylhydrazide of the corresponding 2 : 3 : 6-tri-*O*-methyl-D-mannonic acid.

Fraction 4 was further separated into a trimethylmannose (6·8%) and a dimethylmannose (1·2%). The trimethylmannose, which was chromatographically pure, crystallised to give a non-reducing hexamethyl-disaccharide *X*, m. p. 148—150°, $[\alpha]_D^{18}$ +55° (*c*, 1·4 in $H_2O$). The substance *X* was methylated and gave on hydrolysis only 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose, indicating that both mannose residues were in the pyranose form. The trimethylmannose was regenerated on hydrolysis of substance *X* and travelled on the chromatogram at a speed different from 2 : 3 : 6- and 3 : 4 : 6-tri-*O*-methylmannoses. Oxidation with lead tetra-acetate showed that the sugar could not be 2 : 4 : 6-tri-*O*-methylmannose, and the detection of formadehyde on oxidation with sodium metaperiodate (Chanda, Hirst, Percival, and Ross, *J.*, 1952, 1833) indicated that the sugar was 2 : 3 : 4-tri-*O*-methyl-D-mannose. The non-reducing substance *X* was therefore 2 : 3 : 4-tri-*O*-methyl-D-mannopyranosyl 2 : 3 : 4-tri-*O*-methyl-D-mannopyranoside. The dimethyl sugar travelled on the chromatogram at the same rate as 2 : 3-di-*O*-methyl-D-mannose, but the small quantity isolated was of little structural significance and probably arose from undermethylation of the polysaccharide and/or demethylation during hydrolysis. No methylated glucoses were isolated.

Although it was not found possible to obtain a complete paper chromatographic separation of all the methylated sugars, hypoiodite oxidation (cf. Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289) indicated a ratio of tetramethyl sugar : trimethyl sugar of 1 : 9, a figure in close agreement with the quantities of methylated sugars isolated from the column.

The isolation of tetramethylgalactose (1·7%) accounted for all the galactose present in the original polysaccharide. The isolation of both tetramethylmannose and tetramethylgalactose together with the absence of significant quantities of any dimethyl sugar indicates that at least two molecular types are present in mannan A, both comprising an average of 10—13 mannose residues, one terminated at the non-reducing end by a mannopyranose residue and the other by a galactopyranose residue. From the present evidence, it is not possible to indicate whether 1 : 6-linked mannose residues are randomly distributed in both molecular types or are present only in one. The stability of mannan A to acid hydrolysis together with its optical rotation indicates that the majority of mannose residues are joined by β-1 : 4-linkages.

Mannan B was isolated by dissolution of the residue after extraction of mannan A in cuprammonium solution and precipitation by the addition of sodium hydroxide solution, and purified by dissolution in anhydrous formic acid. The mannan gave on hydrolysis D-mannose (98·3%), D-galactose (1·1%), and D-glucose (0·8%).

Methylation of the polysaccharide gave methylated mannan B, which was hydrolysed as before to give a mixture of methylated sugars, separation of which gave the following fractions: (1*a*) 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose (1·3%); (1*b*) 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (1·3%); (2) 2 : 3 : 6-tri-*O*-methyl-D-mannose (81·8%); (3) and (4*a*) 2 : 3 : 4-tri-*O*-methyl-D-mannose (14·3%); and (4*b*) 2 : 3-di-*O*-methyl-D-mannose (1·3%). Paper chromatographic estimation indicated a ratio of tetramethyl sugar : trimethyl sugar of 1 : 40, a value in close agreement with the quantities of methylated sugars isolated from the column.

As in the case of mannan A, all the galactose residues of mannan B were accounted for as tetramethylgalactose. The isolation of both tetramethylmannose and tetramethylgalactose may be explained in two ways: (*a*) mannan B consists of equal amounts of two

molecular species of average chain length 38—40, terminated at the non-reducing end by mannopyranose and galactopyranose residues, respectively; (*b*) mannan B consists of a singly branched molecule of 75—80 D-mannopyranose residues, one of the two non-reducing end groups being a galactopyranose residue. In the absence of a physical determination of molecular size it is impossible to distinguish finally between these two alternatives, but as at least part of the dimethylmannose isolated probably arose from undermethylation of the polysaccharide and/or demethylation during hydrolysis, the first explanation seems more probable.

The results of the present investigation indicate that mannans A and B are chemically similar and differ only in molecular size, having average chain lengths of 10—13 and 38—40, respectively. It is probable that both mannans contain at least two molecular types differing in the terminal non-reducing sugar residue. Further investigations will be necessary in the case of both mannans to decide whether the 1 : 6-linked mannose residues are regularly or randomly distributed.

## Experimental

### *Mannan A*

*Preparation of Mannan A.*—Ivory nut shavings were extracted successively with benzene and methanol to remove waxy and colouring materials, and were delignified by Wise's method (*Ind. Eng. Chem. Anal.*, 1945, **17**, 63) as modified by Chanda, Hirst, Jones, and Percival (*loc. cit.*). The holocellulose was extracted with potassium hydroxide solution (7%), the extract acidified with glacial acetic acid, and the crude mannan precipitated by the addition of an equal volume of ethanol. The polysaccharide, obtained in 42% yield after 3 extractions, had $[\alpha]_D^{13}$ −39° (*c*, 1·0 in N-NaOH). Purification was effected by two successive precipitations of the copper complex formed on addition of Fehling's solution to a solution of the polysaccharide in aqueous potassium hydroxide (7%), followed by decomposition of the copper complex with dilute hydrochloric acid and precipitation of the regenerated polysaccharide with ethanol. The purified mannan A had $[\alpha]_D^{15}$ −46° (*c*, 0·7 in N-NaOH), and $[\alpha]_D^{15}$ −28° (*c*, 0·8 in anhydrous formic acid; unchanged after 70 hr.). Chromatographic examination of the hydrolysate (Hirst and Jones, *loc. cit.*; Duff and Eastwood, *loc. cit.*) showed the presence of mannose (97·6%), galactose (1·8%), and glucose (0·8%).

*Methylation of Mannan A.*—Mannan A (20 g.) was methylated eleven times with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature and once with methyl iodide and silver oxide, giving a product (9 g.; Found: OMe, 43·5%), isolated by dissolution in hot chloroform.

Fractionation was effected by refluxing chloroform–light petroleum (b. p. 60—65°) mixtures of differing composition. Two main fractions were obtained and these were combined for subsequent work.

| Fraction | % $CHCl_3$ in solvent | $[\alpha]_D^{17}$ (*c*, 1·0 in $CHCl_3$) | OMe, % | Wt. (g.) |
|---|---|---|---|---|
| 1 | 10 | −22° | 44·4 | 2·66 |
| 2 | 15 | −23 | 44·2 | 4·80 |

*Hydrolysis of Methylated Mannan A.*—Methylated mannan A (4 g.) was heated with anhydrous formic acid (25 c.c.) at 100° for 8 hr. The formic acid was removed under reduced pressure and the resultant syrup heated with N-sulphuric acid (10 c.c.) on the water-bath for 6 hr. to hydrolyse formyl esters and neutralised with Amberlite resin IR-4B, and the solution concentrated to a syrup. Paper chromatographic examination, butanol–ethanol–water (4 : 1 : 5; top layer) being used as solvent, showed the presence of tetramethylmannose and trimethylmannose, together with smaller quantities of tetramethylgalactose and a dimethylmannose.

*Separation of Methylated Sugars and Examination of Fractions.*—The syrupy hydrolysate (3·43 g.) was fractionated on cellulose (90 × 3 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum (b. p. 100—120°)–*n*-butanol (6 : 4), saturated with water, as eluant to give four fractions.

*Fraction* 1. The syrup (242 mg.) was partly crystalline and after recrystallisation from ether had m. p. 109—111°. The mixture of syrup and crystals had $[\alpha]_D^{20}$ +23° ⟶ +10° (*c*, 0·7 in $H_2O$) (Found: OMe, 50·4. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). Chromatographic examination showed only 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose, and the aniline derivative

had m. p. 144—145° (not depressed on admixture with an authentic sample) and $[\alpha]_D^{18}$ −94° ⟶ −42° (*c*, 0·8 in $COMe_2$) (Found: C, 61·8; H, 8·0. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·0%). A portion of the syrup was converted into the δ-lactone {$[\alpha]_D^{15}$ +148° (*c*, 1·0 in $H_2O$)} which was characterised by conversion into 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannonic acid phenylhydrazide, m. p. and mixed m. p. 185—186° (Found: N, 7·8. Calc. for $C_{16}H_{26}O_6N_2$: N, 8·2%).

*Fraction* 2. The syrup (58 mg.) was chromatographically pure and was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 195—196°, $[\alpha]_D^{16}$ −136° (*c*, 0·4 in $C_5H_5N$), $[\alpha]_D^{14}$ −76° (*c*, 0·3 in $COMe_2$).

*Fraction* 3. The syrup (2·623 g.) had $[\alpha]_D^{13}$ −7° (*c*, 4·6 in $H_2O$) (Found: OMe, 38·6. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Chromatographic examination showed only 2 : 3 : 6-tri-*O*-methylmannose, and hypoiodite oxidation indicated 92% purity. A sample was converted into 2 : 3 : 6-tri-*O*-methyl-*N*-phenyl-D-mannosylamine, m. p. and mixed m. p. 127—128°. A second sample was converted into the γ-lactone, m. p. and mixed m. p. 81—82°, $[\alpha]_D^{15}$ +64·5° (*c*, 3·2 in $H_2O$), part of which was converted into 2 : 3 : 6-tri-*O*-methyl-D-mannonic acid phenylhydrazide, m. p. and mixed m. p. 132—133°.

*Fraction* 4. Paper chromatography showed the presence of two sugars, and the syrup (240 mg.) was separated on Whatman 3MM paper with butanol–ethanol–water (4 : 1 : 5; top layer) as eluant to give fractions (4*a*) (206 mg.) and (4*b*) (34 mg.). Fraction 4*a*, obtained as a syrup, travelled on the chromatogram as a trimethylhexose but at a speed different from those of 2 : 3 : 6- and 3 : 4 : 6-tri-*O*-methylmannoses. After several weeks the syrup crystallised almost completely to a non-reducing *substance X*, m. p. 148—150°, $[\alpha]_D^{18}$ +55° (*c*, 1·4 in $H_2O$, unchanged after 48 hr.), $[\alpha]_D^{18}$ +65° (*c*, 0·7 in 1% methanolic hydrogen chloride, unchanged after 100 hr.) (Found: C, 50·5; H, 7·9; OMe, 42·9. $C_{18}H_{34}O_{11}$ requires C, 50·7; H, 8·0; OMe, 43·7%). Demethylation (Hough, Jones, and Wadman, *J.*, 1950, 1702) showed *X* to be a mannose derivative, and the molecular weight, obtained by Barger's isopiestic method (cf. Caesar, Gruenhut, and Cushing, *J. Amer. Chem. Soc.*, 1947, **69**, 617), corresponded to that of a hexamethyldisaccharide.

Fraction 4*b*, which remained as a syrup, was shown by demethylation to be a mannose derivative and travelled on the chromatogram at the same rate as 2 : 3-di-*O*-methyl-D-mannose.

Substance *X* (60 mg.) was methylated with methyl iodide and silver oxide, and the product (69 mg.) was hydrolysed on the water-bath with sulphuric acid (1 c.c.; N). The hydrolysate was neutralised with Amberlite resin IR-4B and concentrated to a syrup (60 mg.). Chromatographic examination showed only tetramethylmannose, and the syrup was converted into 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-mannosylamine (70 mg.), m. p. and mixed m. p. 144—145°.

Hydrolysis of *X* gave a chromatographically pure trimethylmannose which was oxidised by lead tetra-acetate (cf. Buchanan, Dekker, and Long, *J.*, 1950, 3162). Oxidation with sodium metaperiodate solution liberated formaldehyde, which was detected with phenylhydrazine hydrochloride, potassium ferricyanide, and concentrated hydrochloric acid (cf. Chanda, Hirst, Percival, and Ross, *loc. cit.*). The trimethylmannose was therefore 2 : 3 : 4-tri-*O*-methyl-D-mannose, and X was 2 : 3 : 4-*tri*-O-*methyl*-D-*mannopyranosyl* 2 : 3 : 4-*tri*-O-*methyl*-D-*mannopyranoside*.

*Quantitative Examination of the Methylated Sugars.*—A portion of the hydrolysate of methylated mannan A was separated chromatographically (Hirst, Hough, and Jones, *J.*, 1949, 298), benzene–ethanol–water (169 : 47 : 15; top layer) being used as solvent, and the tetramethyl and trimethyl sugars estimated by alkaline hypoiodite (cf. Chanda, Hirst, Jones, and Percival, *loc. cit.*) [Found (results expressed as c.c. of 0·01N-iodine consumed): "tetra," 0·16, 0·41; "tri," 1·43, 3·68]. These figures correspond to a molecular ratio of tetramethyl sugars : trimethyl sugars of 1 : 9.

### *Mannan B*

*Preparation of Mannan B.*—The residue remaining after extraction of mannan A was extracted with potassium hydroxide solution (14%) to remove further mannan A, washed with water to remove alkali, and shaken in the dark with cuprammonium solution to which sucrose had been added to minimise oxidation of the polysaccharide. After removal of undissolved materials at the centrifuge, sodium hydroxide solution was added until the mixture was 0·2N with respect to sodium hydroxide. The bulky complex which separated was stirred with water and decomposed with glacial acetic acid, the mannan being precipitated by the addition of an equal volume of ethanol. The material thus obtained was subjected to a second precipit-

ation by the same procedure and crude mannan B isolated. Chromatographic examination of the hydrolysate showed the presence of mannose, glucose, and galactose. Further purification was effected by re-extraction with potassium hydroxide solution (7%) followed by dissolution in anhydrous formic acid (Dr. J. K. N. Jones, personal communication), mannan B {$[\alpha]_D^{15}$ −26° (*c*, 0·8 in anhydrous formic acid, unchanged after 70 hr.)} being obtained by precipitation with ethanol. Chromatographic examination of the hydrolysate showed the presence of mannose (98·3%), galactose (1·1%), and glucose (0·8%).

*Methylation of Mannan B.*—Mannan B (11 g.) was methylated 12 times with methyl sulphate and sodium hydroxide and twice with methyl iodide and silver oxide to give a product (3·5 g.; Found: OMe, 44·9%) isolated by dissolution in hot chloroform. Fractionation by dissolution in chloroform–light petroleum mixtures gave a main fraction {2·8 g.; $[\alpha]_D^{15}$ −20° (*c*, 1·0 in $CHCl_3$); Found: OMe, 45·0%}.

*Hydrolysis of Methylated Mannan B and Separation of Methylated Sugars.*—Methylated mannan B (2·5 g.) was hydrolysed successively with anhydrous formic acid (15 c.c.) and sulphuric acid (7 c.c.; N) as described for methylated mannan A. The hydrolysate (2·0 g.) was fractionated on cellulose as described previously and four fractions collected.

*Fraction* 1. Chromatographic examination of the syrup (55 mg.) showed the presence of two sugars, which were separated on Whatman 3MM paper with benzene–ethanol–water as eluant to give fractions 1*a* (27 mg.) and 1*b* (28 mg.). Fraction 1*a* was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose by conversion into its aniline derivative, m. p. and mixed m. p. 144—145°, $[\alpha]_D^{17}$ −96° ⟶ −41° (*c*, 0·1 in $COMe_2$). Fraction 1*b* was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose by conversion into its aniline derivative, m. p. and mixed m. p. 195—196°, $[\alpha]_D^{16}$ −137° (*c*, 0·5 in $C_5H_5N$).

*Fraction* 2. The syrup (1·640 g.) had $[\alpha]_D^{17}$ −10° (*c*, 6·0 in $H_2O$). Chromatographic examination showed only 2 : 3 : 6-tri-*O*-methyl-D-mannose, and hypoiodite oxidation indicated 95% purity (Found: OMe, 39·8. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). The identity of the sugar was confirmed by conversion into 2 : 3 : 6-tri-*O*-methyl-*N*-phenyl-D-mannosylamine, m. p. and mixed m. p. 127—128°, $[\alpha]_D^{16}$ −155° ⟶ −40° (*c*, 0·1 in MeOH) (Found: C, 60·9; H, 7·9; N, 4·1. Calc. for $C_{15}H_{23}O_5N$: C, 60·6; H, 7·8; N, 4·7%), 2 : 3 : 6-tri-*O*-methyl-D-mannono-γ-lactone, m. p. and mixed m. p. 80—81°, $[\alpha]_D^{20}$ +69·5° (*c*, 0·6 in $H_2O$), and 2 : 3 : 6-tri-*O*-methyl-D-mannonic acid phenylhydrazide, m. p. and mixed m. p. 130—131°, $[\alpha]_D^{16}$ −17° (*c*, 0·4 in $H_2O$).

*Fraction* 3. The syrup (66 mg.) crystallised slowly and after recrystallisation from ether had m. p. 149—151° (undepressed on admixture with fraction 4*a* of the methylated mannan A hydrolysate).

*Fraction* 4. The syrup (232 mg.) which partly crystallised on standing was hydrolysed with N-sulphuric acid, and chromatographic examination showed the presence of two sugars. Separation was effected on Whatman 3MM paper, butanol–ethanol–water being used as eluant to give fractions 4*a* (203 mg.) and 4*b* (29 mg.). Fraction 4*a* had m. p. 148—150° (undepressed on admixture with fraction 3). Fraction 4*b* was demethylated to give mannose and travelled on the chromatogram at the same rate as 2 : 3-di-*O*-methyl-D-mannose.

*Quantitative Examination of the Methylated Sugars.*—A portion of the hydrolysate of methylated mannan B was separated chromatographically and estimated by alkaline hypoiodite as described previously [Found (results expressed as c.c. of 0·01N-iodine consumed): "tetra," 0·085, 0·075; "tri," 3·50, 2·96]. These figures correspond to a molecular ratio of tetramethyl sugar : trimethyl sugar of 1 : 40.

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# 636. *The Thermochemistry of Organo-arsenic Compounds. Part III.* Phenylarsine.*

By C. T. Mortimer and H. A. Skinner.

The heat of reaction at 25° of liquid phenylarsine with iodine (dissolved in carbon tetrachloride) to yield a solution of phenylarsenic di-iodide and hydrogen iodide has been measured: $\Delta H_{obs.} = -31{\cdot}0 \pm 1$ kcal./mole. From this, one may derive $\Delta Hf°$ ($PhAsH_2$, liq.) − $\Delta Hf°$ ($PhAsI_2$, liq.) = $22{\cdot}9 \pm 1{\cdot}7$ kcal./mole.

The *difference* between the mean bond-dissociation energies of the As–H and As–I bonds in phenylarsine and in phenylarsenic di-iodide is obtained ($\Delta\overline{D} = 17{\cdot}0 \pm 2{\cdot}3$ kcal./mole), and is very close to the corresponding difference between the bonds in arsine and in arsenic tri-iodide.

According to Blicke and Powers (*J. Amer. Chem. Soc.*, 1933, **55**, 1161), one mol. of phenylarsine, dissolved in ether, reacts instantly with two mols. of iodine to give a quantitative yield of phenylarsenic di-iodide:

$$PhAsH_2 + 2I_2 \longrightarrow PhAsI_2 + 2HI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The same reaction—to the extent of at least 98%—was observed in benzene as solvent.

The quantitative nature, and the rapidity, of reaction (1) made it seem probable that the reaction might be amenable to thermal study, but several difficulties were encountered before we developed a satisfactory method of handling the reaction in a calorimeter. These difficulties arise from (i) the extreme reactivity of phenylarsine, particularly towards oxygen and oxidants, thus necessitating an inert atmosphere, and a dry solvent of high purity, and (ii) the generally low solubility of hydrogen iodide in inert solvents. Pyridine appeared likely to be a satisfactory solvent, in that it readily absorbs hydrogen iodide, and several experiments were carried out in that solvent. However, a satisfactory reproducibility in the thermal results was not attained; this may be due to the well-known difficulty of obtaining pyridine in a pure dry state. Some reactions in methanol suggested that the reaction in this solvent does not follow eqn. (1) and that the methanol enters into reaction at some stage of the iodination. The uptake of iodine by phenylarsine in methanol was found to be less than required by the reaction (1), and experiments using this solvent were abandoned.

Satisfactorily reproducible results were obtained by using pure dry carbon tetrachloride as solvent. From blank experiments outside the calorimeter it was found that the reaction in carbon tetrachloride proceeds to at least 98% completion according to eqn. (1).

## Experimental

*Preparation of Compounds.*—Phenylarsine was prepared by reduction of phenylarsonic acid, as described by Palmer and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 1356), *viz.*:

$$PhAsO(OH)_2 + 3H_2 \longrightarrow PhAsH_2 + 3H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The reduction was carried out in ethereal solution with zinc dust and concentrated hydrochloric acid. The ethereal layer was separated, washed with dilute aqueous sodium hydrogen carbonate, and dried ($CaCl_2$). All operations were performed in an inert atmosphere. The product was separated from the ether by distillation and, purified by fractional distillation through a 6″ steel-gauze packed column, had b. p. 44·8—45·0°/5·5 mm. The pure product was finally distilled in a high vacuum and collected and sealed in thin, weighed, glass ampoules. Phenylarsenic di-iodide was prepared by Steinkopf and Smie's method (*Ber.*, 1926, **59**, 1461). The crude oil was purified by recrystallization from cooled alcohol.

Carbon tetrachloride of "AnalaR" (medicinal) grade was degassed, saturated with nitrogen, and dried ($CaCl_2$) before use in the calorimeter.

* Part II, *J.*, 1953, 1181.

*Calorimeter.*—The calorimeter has been described by Mortimer and Skinner (*J.*, 1952, 4331). The experiments were performed by breaking the ampoules containing known amounts of phenylarsine under the surface of 750 c.c. of carbon tetrachloride (containing dissolved iodine) in the Dewar vessel. An excess of iodine—normally 10% excess on the requirement of eqn. (1)—was used to assist completion of the reaction. The whole Dewar assembly was flushed with pure dry nitrogen before the experiments were started, and a slow steady stream of nitrogen was maintained in the head-piece of the Dewar calorimeter throughout each run. Temperature changes were followed by the resistance change in a shielded thermistor element immersed in the reaction solution. The calorimeter was calibrated electrically by the substitution method.

*Units.*—All heat quantities are given in units of the thermochemical calorie, 1 cal. = 4·1840 abs. joule. The reactions were performed at 25°.

*Results.*—The observed heat of reaction, $\Delta H_{obs.}$, refers to the system

$$PhAsH_2(liq.) + 2I_2(CCl_4\ soln.) \longrightarrow \{PhAsI_2 + 2HI\}\ (CCl_4\ soln.) \quad . \quad . \quad . \quad . \quad (3)$$

From six experiments, with quantities of phenylarsine in the range 0·4—0·6 g., and 10% excess of iodine in each case, the mean value $\Delta H_{obs.} = -31{\cdot}0$ kcal./mole was obtained, subject to a possible error of ±1 kcal./mole.

$\Delta H_{obs.}$ incorporates the heat terms arising from the solution of iodine, phenylarsenic di-iodide, and hydrogen iodide in carbon tetrachloride. Hartley and Skinner (*Trans. Faraday Soc.*, 1950, **46**, 621) have reported $\Delta H_{soln.}$ ($I_2$, $CCl_4$) = 5·8 ± 0·2 kcal./mole, and their value is used here. The heat of solution of gaseous hydrogen iodide in carbon tetrachloride was measured directly, $\Delta H_{soln.}$ (HI, $CCl_4$) = −4·9 ± 0·1 kcal./mole. The heat of solution of phenylarsenic di-iodide in carbon tetrachloride containing iodine * (equivalent in amount to the excess of iodine remaining in solution on completion of the reaction) was measured independently: $\Delta H_{soln.}$($PhAsI_2$, $CCl_4$) = 0·9 ± 0·05 kcal./mole. For the idealized reaction:

$$PhAsH_2(liq.) + 2I_2\ (cryst.) \longrightarrow PhAsI_2(liq.) + 2HI\ (g.) \quad . \quad . \quad . \quad . \quad . \quad (4)$$

one may then derive $\Delta H = -10{\cdot}5 \pm 1{\cdot}7$ kcal./mole. From this, and the value $\Delta Hf^\circ$ (HI, g.) = 6·20 kcal./mole (Nat. Bur. Stand. Circular 500, 1952), it follows that

$$\Delta Hf^\circ(PhAsH_2, liq.) - \Delta Hf^\circ(PhAsI_2, liq.) = 22{\cdot}9 \pm 1{\cdot}7\ kcal./mole \quad . \quad . \quad . \quad . \quad (5)$$

## Discussion

Equation (5) serves as a starting-point from which the difference between the As–H and As–I bond energies in these compounds may be derived. We use the symbol $\overline{D}$(As–H) to represent the *mean* bond dissociation energy of the As–H bonds in phenylarsine, where $\overline{D}$(As–H) is defined from

$$PhAsH_2\ (g.) \longrightarrow PhAs\ (g.) + 2H\ (g.);\ \Delta H = 2\overline{D}(As\text{–}H) \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Correspondingly, $\overline{D}$(As–I) in phenylarsenic di-iodide is defined from

$$PhAsI_2\ (g.) \longrightarrow PhAs\ (g.) + 2I\ (g.);\ \Delta H = 2\overline{D}(As\text{–}I) \quad . \quad . \quad . \quad . \quad . \quad (7)$$

By combining eqns. (6) and (7), and using the well-established values $\Delta Hf^\circ$ (H, g.) = 52·1 and $\Delta Hf^\circ$ (I, g.) = 25·5 kcal./mole (N.B.S. Circular 500), one can express the difference between $\overline{D}$(As–H) and $\overline{D}$(As–I) by the equation

$$\Delta\overline{D}\begin{bmatrix}As\text{–}H\\As\text{–}I\end{bmatrix} = 26{\cdot}6 + \tfrac{1}{2}\Delta Hf^\circ\ (PhAsI_2, g.) - \tfrac{1}{2}\Delta Hf^\circ(PhAsH_2, g.) \quad . \quad . \quad . \quad . \quad (8)$$

Equation (5) enables us to eliminate the terms in $\Delta Hf^\circ$ from eqn. (8), and obtain

$$\Delta\overline{D}\begin{bmatrix}As\text{–}H\\As\text{–}I\end{bmatrix} = 15{\cdot}1\ (\pm 0{\cdot}8) + \tfrac{1}{2}(\lambda_1 - \lambda_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where $\lambda_1 = -\Delta H_{vap.}(PhAsI_2)$ and $\lambda_2 = -\Delta H_{vap.}(PhAsH_2)$. The value of $\lambda_2$ may be estimated at 12·7 ± 1 kcal./mole from our own and other vapour-pressure data quoted by

* There is a small heat of mixing of phenylarsenic di-iodide with dissolved iodine. The heat of solution of phenylarsenic di-iodide in pure carbon tetrachloride alone was measured as: $\Delta H_{soln.}$ = 1·64 ± 0·05 kcal./mole.

Goddard (Newton-Friend's "Textbook of Inorganic Chemistry," Vol. II, Part 2, 1930, p. 63, Griffin & Co. Ltd.). The vapour-pressure data on phenylarsenic di-iodide are too scanty to allow a direct estimate of $\lambda_1$, but a rough value may be got as follows; from Redemann, Chaikin, Fearing, and Benedict's vapour-pressure data (*J. Amer. Chem. Soc.*, 1948, **70**, 637) on phenylarsenic dichloride, the latent heat of vaporization may be calculated: $\lambda_{vap.}(PhAsCl_2) = 13{\cdot}9$ kcal./mole. This corresponds to a value of 26·6 for the Trouton constant, and if we now carry this over to the case of phenylarsenic di-iodide, we then obtain $\lambda_1 \cong 16{\cdot}4$ kcal./mole. After allowance for a possible error of $\pm 2$ kcal./mole in this estimate of $\lambda_1$, eqn. (9) becomes

$$\Delta\bar{D}\begin{bmatrix}\text{As–H}\\ \text{As–I}\end{bmatrix} = 17{\cdot}0 \pm 2{\cdot}3 \text{ kcal./mole} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Mortimer and Skinner (*J.*, 1952, 4331) have given values for the mean bond-dissociation energy in arsine, $\bar{D}(\text{As–H}) = 58{\cdot}6$ kcal./mole, and in arsenic tri-iodide, $\bar{D}(\text{As–I}) = 42{\cdot}6$ kcal./mole, from which the difference $\Delta\bar{D}\begin{bmatrix}\text{As–H}\\ \text{As–I}\end{bmatrix} = 16{\cdot}0$ kcal./mole results, in close agreement with the corresponding value of $\Delta\bar{D}$ given in eqn. (10).

We shall describe the molecule phenylarsine as a "mixed" molecule, derived from the "parent" molecules arsine and triphenylarsine; similarly, the parents of phenylarsenic di-iodide are arsenic tri-iodide and triphenylarsine. A general thermochemical problem of mixed molecules may now be formulated: how far can values appropriate to the parents be carried over unchanged to the mixed molecule? The present investigation suggests that in the mixed molecules $PhAsX_2$ the values $\bar{D}(\text{As–X})$ are transferable from the parents $AsX_3$.

From measurements of the heats of reaction of diphenylmercury with the mercuric halides, Hartley, Pritchard, and Skinner (*Trans. Faraday Soc.*, 1951, **47**, 254) concluded that the $\bar{D}$ values in phenylmeruric iodide are, within small error limits, transferable from the parents. In phenylmercuric bromide and chloride, the $\bar{D}$ values are enhanced by a few kcal./mole above the parent values. In the alkylmercuric halides, RHgX (R = Me, Et, Pr, Pr$^i$), the $\bar{D}$ values are enhanced appreciably over the parent values.

Mortimer and Skinner (*loc. cit.*) obtained a value for $\bar{D}(\text{As–I})$ in cacodyl iodide, which is higher by 4—6 kcal./mole than $\bar{D}(\text{As–I})$ in arsenic tri-iodide. Skinner and Tees (*J.*, in the press), from studies on the dibutylboron halides, expressed the view that in these compounds the $\bar{D}(\text{B–Bu})$ values are enhanced over the parent value. The evidence at present suggests that, in the mixed compounds of the general type $R_nMX_m$, where M is the $(n + m)$-valent central atom, the $\bar{D}$ values are transferable from the parents when R = Ph and X = H or I, but that enhancement occurs in one or more of the $\bar{D}$ values when R = alkyl and X = halogen.

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## 637. *The Stability of Transition-metal Complexes.*

By H. Irving and R. J. P. Williams.

Published and original data on the stability of complexes formed by bivalent ions of the first transition series have been collected and examined critically. The order Mn < Fe < Co < Ni < Cu > Zn has been found to hold for the stability of nearly all such complexes irrespective of the nature of the co-ordinated ligand or of the number of ligand molecules involved. A theoretical justification for this stability order follows from considerations of the reciprocal of the ionic radii and the second ionisation potentials of the metals concerned, and it is shown why other (empirical) orders, or stability orders which include other elements, can have no general validity.

The extent to which variations in characteristic co-ordination number, stereochemical considerations, and entropy factors may affect such a stability order is discussed theoretically and illustrated by examples. Changes in bonding orbitals concomitant with changes in the nature of the ligand are shown to lead to certain complexes of anomalously high stability, notably in the case of ferrous ions.

Although studies of the relative stabilities of solid complex salts and co-ordination compounds are almost inevitably complicated by considerations of lattice energy, yet with certain specialised types, *viz.*, the solid adducts of electron-deficient molecules of the type $BF_3$ or $MR_3$ (where M = Group III metal and R = alkyl) with donor molecules of the type $AR_2$ (where A = O, Se, and Te) or $BR_3$ (where B = N, P, As, etc.), measurements of dissociation pressures have provided thermodynamic data of great theoretical interest (Brown *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 431; 1947, **69**, 1332; 1948, **70**, 2848; Coates, *J.*, 1951, 2003; *Quart. Reviews*, 1950, **4**, 217; cf. Kabesh and Nyholm, *J.*, 1951, 3245).

Although the disturbing features of lattice energy can be avoided by measurements of complex stabilities in homogeneous solution the systems become complicated in other respects, for the formation of any complex $ML_n$ from a metal M and a ligand L must proceed stepwise through such successive stages as

$$M + L \rightleftharpoons ML;\ ML + L \rightleftharpoons ML_2;\ \ldots\ ML_{n-1} + L \rightleftharpoons ML_n$$

and, since all the species $ML_n$, $N$ being the maximum co-ordination number are in mutual equilibrium, the full description of such systems demands a knowledge of $n$ equilibrium constants (otherwise termed complexity or formation constants) defined by $K_n = [ML_n]/[ML_{n-1}][L]$. [For the sake of generality the charges on dissolved species and any indication of their relative degrees of hydration are omitted; and while L may be a mono- or a poly-dentate ligand it is assumed that the solution contains no polynuclear complexes and no complexes in which ligands of more than one type (excluding water) are bound to the same metal atom.] Quite apart from the freedom from lattice effects, equilibrium studies in solution chemistry have certain unique advantages in that they permit the evaluation of the stabilities of individual members of groups of closely related and chemically very similar compounds [*e.g.*, the hydrated ions $Ni(NH_3)_n,aq.,^{++}$ $n = 0$—6] which may not be capable of isolation in the pure state at all—inasmuch as they exist only in solution and in dynamic equilibrium with other species.

The concentration of free metal ions in solution in a system where the total metal concentration is $C_M$ and the free ligand concentration is [L] is readily shown (Bjerrum, "Metal Ammine Formation in Aqueous Solution," Copenhagen, 1941) to be

$$[M] = C_M/\Sigma_0^n \beta_n[L]^n, \text{ where } \beta_n = K_1K_2 \ldots K_n \text{ and } \beta_0 = 1$$

The effect of complex formation in changing this concentration of free metal ion is of the greatest importance in analytical chemistry where it is exploited in "masking" and "de-masking" reactions (cf. Feigl, "The Chemistry of Specific, Selective, and Sensitive Reactions," New York, Academic Press Inc., 1949); it is fundamental to discussions of the pH of precipitation of metal hydroxides, sulphides, and organic complexes (Irving and

Williams, *Analyst*, 1952, **77**, 813) and to any quantitative treatment of solvent extraction (cf. Irving, *Quart. Reviews*, 1951, **5**, 200); it will modify the kinetics of metal-catalysed decarboxylations and similar reactions (cf. p. 3196), and may be the dominant feature in those biological systems where trace metals play a vital rôle (Williams, *Biol. Reviews*, in the press). Where metals display more than one valency state, complexing by any given ligand favours one state rather than the other, and the resultant changes in redox potential are again of importance in biochemical as well as in analytical and purely theoretical discussions. Since, in general, two or more different metals will form complexes of unequal stability with one and the same ligand, possibilities of analytical separations arise; and should the ligand be an organic reagent of suitable molecular geometry, it may happen that relatively few metals, or at best only one, will form a strong chelate complex with it so that its use as a selective or " singular " reagent—or even as a truly specific reagent—could be realised (Irving and Williams, *loc. cit.*).

In all these fields a knowledge of the magnitude of the stability constants of complexes is a necessary preliminary to quantitative treatment. But since these constants are also a measure of free-energy changes (in view of the relationship $-\Delta G = 2{\cdot}303RT \log_{10}\beta$), there ought to be some correlation with the strength of the metal–ligand bonds to which these constants can be referred—and hence to those fundamental properties of the metal ion and ligand molecule which control the type and the strength of the bonding involved. Somewhat restricted relationships have been traced between complex stability and the basic strength of the ligand employed (cf. Bjerrum, *Chem. Reviews*, 1950, **46**, 381, and refs. therein) but the part played by the metal has received little attention.

*Available Data.*—Many values have been pubished for the formation (complexity) constants of various metal–ligand systems, especially in recent years, but the experimental methods employed and the precision attained have varied considerably. Some authors have worked at unspecified " room temperature " and with solutions in which the ionic strength must have varied appreciably during the experiments and can only be estimated approximately from their figures. The data of others refer almost exclusively to one fixed temperature, often 25·0°, and to solutions containing a salt " background " of known ionic strength; in the best work (*e.g.*, by Schwarzenbach) corrections are made for any competitive complexing between metal and anions present. The order of magnitude of effects caused by changes in temperature or ionic strength may be inferred from the following formula given by Bjerrum (*op. cit.*) to represent his data for the copper–ammonia system in ammonium nitrate (or chloride) solutions of concentration up to 5N :

$$\log K_n = \log K_n^\circ + 0{\cdot}080[NH_4NO_3] + 0{\cdot}013(30^\circ - t^\circ)$$

where $\log K_1^\circ = 3{\cdot}99$, $\log K_2^\circ = 3{\cdot}34$, $\log K_3^\circ = 2{\cdot}73$, and $\log K_4^\circ = 1{\cdot}97$. Values of $d(\log K_n)/dT$ for various transition-metal complexes with ethylenediamine (present authors; unpublished observations), diethylenetriamine (Jonassen, LeBlanc, Meibohm, and Rogan, *J. Amer. Chem. Soc.*, 1950, **72**, 4968), and triethylenetetramine (Jonassen and Meibohm, *J. Phys. Coll. Chem.*, 1951, **55**, 726) range only from 20 to 50 $\times 10^{-3}$, and since the decrement per °C in $\log_{10} K_n$ never exceeds 0·5% of its absolute value, variations in temperature may be ignored for the purpose of the present paper.

Somewhat more disturbing are variations between the results of different workers for the same metal–ligand system; these are illustrated by data in Table 1 for complexes of glycine and alanine with a number of transition metals. To some extent such discrepancies originate from differences in the values adopted for the dissociation constants of the ionic species $^+NH_3{\cdot}R{\cdot}CO_2H$ and $^+NH_3{\cdot}R{\cdot}CO_2^-$, for these are used in the relevant calculations; but this only implies a similar lack of agreement between measurements by different authors of the strength of the corresponding proton amino-acid complexes and emphasises the difficulty of obtaining reliable results for complex stabilities. Fortunately, the same techniques and experimental conditions have generally been used throughout by each individual author when measuring the stabilities either of a series of related ligands with the same metal or of a series of metals with a chosen ligand. For the discussion which follows we have made free use of such sets of data which are likely to be reasonably consistent internally so far as salt-effects, temperature, and intrinsic accuracy are

concerned, and we have avoided drawing conclusions from results obtained under widely different conditions or by methods of low or dubious accuracy. Nevertheless, it must be emphasised that the order of magnitude of effects to which we shall now draw attention in this paper is such that quite considerable experimental uncertainty in the actual values of individual stability constants would not invalidate our conclusions.

Sometimes the low solubility of a metal chelate prevents the use of water as a solvent, and a number of stability constants have been measured in aqueous mixtures with, *e.g.*, alcohol or dioxan. With increasing dioxan content there are significant increases in the measured stability constants of those metal (or proton)–ligand complexes so far studied (Mellor and Maley, *Austral. J. Sci. Res.*, 1949, **2**, 92; Albert, *Proc. Biochem. Soc.*, 1950, **46**, ix; H. Marsh, Thesis, Oxford, 1952), but quantitative correlation with the physical properties of the medium cannot yet be predicted on theoretical grounds, although in recent work (Davies and Monk, *J.*, 1951, 2719) the effect of changes in the dielectric constant of the medium on the dissociation constants of certain metal complexes has received careful study. All measurements which do not refer to pure water as solvent are carefully distinguished in Table 2 and elsewhere.

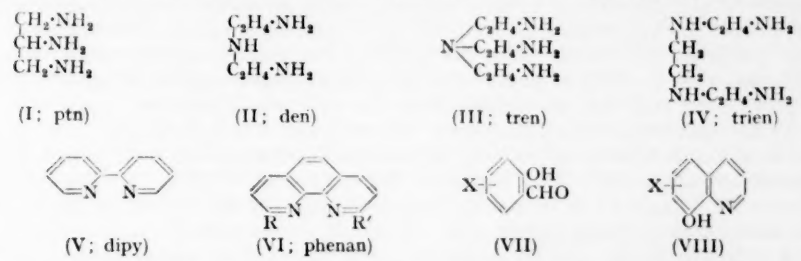
Although individual complexes of a wide variety of elements have been examined quantitatively, the most extensive data refer to two main groups, *viz.*, those of Group II and those of the first transition series. Complexes of Group IIA metals have already been discussed by one of us in a paper (Williams, *J.*, 1952, 3770) originally designed to follow the present paper which will deal predominantly with complexes of elements of atomic number 25—30. Elements of Groups IIB and IIIB will be considered in later papers.

*Orders of Stability.*—Bjerrum (*op. cit.*) did not remark any special features among the values he had determined for the stabilities of ammonia or ethylenediamine complexes of the bivalent transition metals which could be related to properties of the elements concerned. On the other hand, Mellor and Maley (*Nature*, 1947, **159**, 370) reported that the order of decreasing stability of bivalent metal chelates with salicylaldehyde in 50% dioxan, *viz.*, Pd > Cu > Ni > Pb > Co, Zn > Cd > Mg, was the same as that furnished by their then unpublished values for glycine and 8-hydroxyquinoline (as VIII) save that "occasionally the position of neighbouring elements is reversed." The following year (*idem*, *ibid.*, 1948, **161**, 436) the stability order Pd > Cu > Ni > Co > Zn > Cd > Fe > Mn > Mg was shown to hold for ethylenediamine complexes and to be consistent with the sequence of comparative stabilities $Cu^{++} > Ni^{++} > Fe^{+++} > Zn^{++} > Mg^{++}$ noted by Pfeiffer, Thielert, and Glaser (*J. pr. Chem.*, 1939, **152**, 145) for pyridine complexes.

Independently, we observed that if the successive stability constants of complexes of bivalent ions of the first transition series were plotted against the atomic number of the element (cf. Figs. 1 and 4) there was a monotonic increase to a maximum at copper whether the ligands were ammonia, ethylenediamine, propylenediamine, or salicylaldehyde. In a preliminary communication (Irving and Williams, *Nature*, 1948, **162**, 746) we pointed out that this order of stabilities could be intelligibly correlated with the electronic structure and fundamental properties of the ions concerned, notably with the second ionisation potential (cf. p. 3203). The limited range of experimental values then available for the stability constants of transition-metal complexes was supplemented by observations on the pH of incipient precipitation (or 50% precipitation) of certain metal complexes, and the pH of 50% extraction of metal dithizonates. The justification for such correlations which are now realised to be of somewhat limited validity has recently been discussed (Irving and Williams, *Analyst*, 1952, **77**, 813).

Since 1948 there has been intense activity in the field of quantitative solution chemistry and our generalisation that the "natural" order of the stability of complexes of bivalent transition metals is Mn < Fe < Co < Ni < Cu > Zn irrespective of the nature of the ligand has been strikingly confirmed by results now available for a great variety of ligands such as ethylenediamine ($NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$ = en), propylenediamine ($NH_2{\cdot}CHMe{\cdot}CH_2{\cdot}NH_2$ = pn), 1 : 3-diaminopropane ($NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$ = dimp), 1 : 2 : 3-triaminopropane (I; ptn), diethylenetriamine (di-2-aminoethylamine) (II; den), triaminotriethylamine (tri-2-aminoethylamine) (III; tren), triethylenetetramine (IV;

trien), 2 : 2′-dipyridyl (V; dipy), 1 : 10-phenanthroline (phenan; VI; R = R′ = H), a great variety of α- and some β-amino-acids (cf. Fig. 2), and " complexones " such as nitrilotriacetic acid ($NA_3$, where A = $CH_2{\cdot}CO_2H$) * and ethylenediaminetetra-acetic acid (enta acid, $NA_2{\cdot}CH_2{\cdot}CH_2{\cdot}NA_2$), tropolone, and 1 : 3-diketones and β-keto-esters of the type $X{\cdot}CO{\cdot}CH_2{\cdot}COY$, *o*-hydroxyaromatic aldehydes (as VII), 8-hydroxyquinoline and its




derivatives (as VIII), 4-hydroxypteridine (IX), riboflavin (X), folic acid (XI), and many mono- and di-carboxylic acids. Table 2 includes most of the published data and gives values of the individual stability constants log $K_1$, log $K_2$ . . . etc., for the attachment of

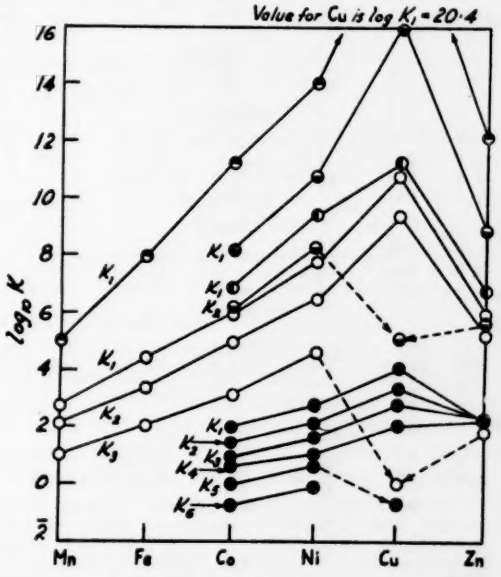



FIG. 1. *The stability of some complexes of the transition metals with nitrogen-type ligands as a function of atomic number.*

- ● *Ammonia. Data valid for* 30° *and* $\mu = 0$.
- ○ *Ethylenediamine. Data valid for* 30° *and* N-KCl.
- ◐ 1 : 2 : 3-*Triaminopropane. Data valid for* 20° *and* $\mu = 0{\cdot}1$.
- ◒ *Diethylenetriamine. Data valid for* 20° *and* $\mu = 0{\cdot}1$.
- ◓ *Triethylenetetramine. Data valid for* 20° *and* $\mu = 0{\cdot}1$.

the first, second, etc., molecule of ligand irrespective of whether it is mono- or poly-dentate. The values of log $\beta_2$ = (log $K_1K_2$), log $\beta_3$ (= log $K_1K_2K_3$), and log $\beta_N$ (= log $K_1K_2 \ldots K_n$), and the gross or over-all stability constants for the attachment of two, three, or $N$ molecules of ligand (again irrespective of its degree of functionality) are quoted in some cases. The order followed is one of increasing complexity through mono-, di-, tri-, to poly-dentate ligands, dealing first with molecules co-ordinated through one or more nitrogen atoms (" nitrogen-type " ligands) followed by chelating parts which include both oxygen and nitrogen bonds (" nitrogen–oxygen-type " ligands), and finally mono- or poly-dentate ligands co-ordinated through oxygen atoms only (" oxygen-type " ligands).

Fig. 1 displays for bivalent metals of the first transition series the variation with atomic number of the stability of complexes with typical monodentate (ammonia), bidentate

* More recent data for polydentate amino-acids will be presented in a later paper.

(ethylenediamine), tridentate (triaminopropane, I; and diethylenetriamine, II), and tetradentate (triethylenetetramine, IV) ligands. The essential feature of this graph—the monotonic rise in stabilities to copper followed by a lower value for zinc, independent of the kind of ligand and of the number of ligands attached (but see p. 3205)—reappears in Fig. 4 and could be reproduced by plotting almost any of the data given in Table 2.

Values for the strengths of metal complexes of a large number of amino-acids given in Tables 1 and 2 are presented graphically in Fig. 2, where the ligands are arranged in order of their published p$K$ values. It is not intended that any special correlation should be noted between the stability of proton- and metal-complexes of any given ligand and it has been pointed out that the measurements are not all of equal precision; some may be in error by as much as 0·5 logarithmic unit. Nevertheless, it is quite obvious that for each one of these dozen ligands the stability of the metal complexes follows the same sequence of metals already noted. This sequence, Mn < Fe < Co < Ni < Cu > Zn, which we shall term the "natural" or Irving–Williams order, remains valid when the basic skeleton of the amino-acid chelating system, *viz.*, :N·C·C·OH, forms part of a heterocyclic system as in 8-hydroxyquinoline and its 5-sulphonic acid (as VIII) or 4-hydroxypteridine (IX), and applies equally to "nitrogen-type," "nitrogen–oxygen-type," and "oxygen-type" ligands (cf. Tables 2 and 1).

*Additional Evidence for the Irving–Williams Order of Stabilities.*—The decarboxylation of the nitroacetate ion, $NO_2{\cdot}CH_2{\cdot}CO_2^-$, is retarded both by protons and by a variety of cations, and Pedersen (*Acta Chem. Scand.*, 1949, **3**, 676) has recently shown that

TABLE 1. *Stability of metal complexes of glycine and alanine.*

(*a*) Glycine, $NH_2{\cdot}CH_2{\cdot}CO_2H$. [a]

| Refs. | Temp. | Manganese | | | Iron | | | Cobalt | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | log $K_1$ | log $K_2$ | log $\beta_2$ | log $K_1$ | log $K_2$ | log $\beta_2$ | log $K_1$ | log $K_2$ | log $\beta_2$ |
| **1, 2** | 20° | 3·2 | 2·3 | 5·5 | 4·29 | 3·66 | 7·95 | 5·06 | 3·85 | 8·91 |
| **3, 4** | 25 | 3·66 | 2·97 | 6·63 | — | — | — | 4·95 | 3·99 | 8·94 |
| **5, 6** | 25 | 3·44 | — | — | — | — | — | 5·23 | 4·02 | 9·25 |
| | | Nickel | | | Copper | | | Zinc | | |
| **1, 2** | 20 | 6·14 | 4·98 | 11·12 | 8·47 | 6·91 | 15·38 | 5·25 | 4·05 | 9·30 |
| **3, 4** | 25 | 6·12 | 5·03 | 11·15 | 8·51 | 6·91 | 15·42 | 5·33 | 4·39 | 9·72 |
| **5, 6** | 25 | 6·18 | 4·96 | 11·14 | 8·62 | 6·97 | 15·59 | 5·52 | 4·44 | 9·96 |

(*b*) α-Alanine, $NH_2{\cdot}CHMe{\cdot}CO_2H$. [b]

| Ref. | Temp. | Manganese | | | Iron | | | Cobalt | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | log $K_1$ | log $K_2$ | log $\beta_2$ | log $K_1$ | log $K_2$ | log $\beta_2$ | log $K_1$ | log $K_2$ | log $\beta_2$ |
| **3, 4** | 25° | 3·24 | 2·81 | 6·05 | — | — | — | 4·83 | 3·95 | 8·78 |
| **5, 6** | 25 | 3·02 | — | — | — | — | — | 4·82 | 3·66 | 8·48 |
| | | Nickel | | | Copper | | | Zinc | | |
| **3, 4** | 25 | — | — | — | 8·18 | 6·65 | 14·83 | 5·16 | 4·34 | 9·50 |
| **5, 6** | 25 | 5·96 | 4·70 | 10·66 | 8·51 | 6·86 | 15·37 | 5·21 | 4·33 | 9·54 |

[1] Albert, personal communication. [2] *Idem, Biochem. J.*, 1950, **47**, 531. [3] Maley and Mellor, *Nature*, 1950, **165**, 453. [4] Mellor and Maley, *Austral. J. Sci. Res.*, 1949, **2**, 579. [5] Monk, *Trans. Faraday Soc.*, 1951, **47**, 285. [6] *Idem, ibid.*, p. 297. [a] Additional values for log $\beta_2$ for copper obtained polarographically are 15·13 ($\mu$ = 0·1) and 15·28 ($\mu$ = 1·0) by Keefer, *J. Amer. Chem. Soc.*, 1946, **68**, 2329; 15·1 ($\mu$ = 0·1) by Laitinen, Onstott, Bailar, and Swann, *ibid.*, 1949, **71**, 1550; and 15·3 ($\mu$ = 1·0) by Irving, Williams, Ferrett, and Williams, paper in preparation. Flood and Loràs (*Tiddskr. Kjemi* 1945, **5**, 83) report for copper at 20°: log $K_1$ = 8·50, log $K_2$ = 6·83, and log $\beta_2$ = 15·33, and at an unspecified temperature (*idem, ibid.*, 1944, **4**, 35): log $\beta_2$ = 10·6 (nickel) and 15·19 (copper). [b] Other values for log $\beta_2$ are 8·4 for cobalt and 15·1 for copper at 20° (ref. 2). Polarographic measurements at 25° give log $\beta_2$ for copper as 15·01 ($\mu$ = 0·1; Keefer, *loc. cit.*) and 14·82 ($\mu$ = 1·0; Li and Doody, *J. Amer. Chem. Soc.*, 1950, **72**, 1891).

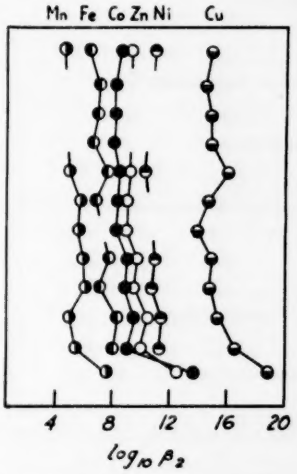
the kinetics can be completely interpreted by postulating that complex formation controls the effective concentration of the decomposing species. The values calculated from kinetic measurements (cf. Table 2) for the stability constants of the metal–nitroacetate ion complex, $(NO_2{\cdot}CH_2{\cdot}CO_2M^{II})^+$, arrange themselves in the order Ba < Ca < Mg < Co < Zn < Ni < Pb < Cd < Be < Cu. On the other hand, the decarboxylation of certain keto-acids (but not the corresponding esters) is positively catalysed by metal ions which are supposed to form complexes involving

a carboxyl group and the carbonyl group of the keto-tautomeride. Data for dimethyloxaloacetic acid, $HO_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2H$, placed the strength of such metal complexes in the order Mn < Fe < Ni < Cu (Steinberger and Westheimer, *J. Amer. Chem. Soc.*, 1949, **71**, 4158; 1951, **73**, 1951), and Prue (*J.*, 1952, 2331) reports the order Mg < Cd < Mn < Pb < Co < Zn < Ni < Be < Cu from kinetic studies of the decarboxylation of acetonedicarboxylic acid. Similarly, the bromination of β-keto-esters is catalysed by metal ions which appear to facilitate proton transfer from ester to base: on the assumption that a small amount of metal complex is formed between the metal ion and the keto-form of ethyl 2-oxo*cyclo*pentanecarboxylate, Pedersen (*Acta Chem. Scand.*, 1948, **2**, 385) has shown that the strength of the metal–ligand complex increases in ths order Mg < Cd < Pb < Zn < Ni < Cu. It will be seen that these stability orders obtained kinetically do not agree completely either with Mellor and Maley's order (p. 3194) or with each other. But without exception the data are consistent with our sequence of stabilities Mn < Fe < Co < Ni < Cu > Zn.

FIG. 2. *Ligands of type* $NH_2{\cdot}CHR{\cdot}CO_2H$.

| Ligand | p*K* |
|---|---|
| Asparagine | 8·9 |
| Serine | 9·15 |
| Methionine | 9·21 |
| Phenylalanine | 9·24 |
| Tryptophan | 9·39 |
| Valine | 9·72 |
| Leucine | 9·74 |
| Glycine | 9·8 |
| D-Alanine | 9·87 |
| Norleucine | 9·96 |
| Proline | 10·60 |
| Histidine | 9·18 |

The points in the Figure, reading from top to bottom, are in the same order as the ligands in the list.




*Absorption Spectra of Metal Complexes.*—On chelation to a metal there is generally a bathochromic shift in the wave-length of maximum absorption of the ligand, and Yamasaki and Sone (*Nature*, 1950, **166**, 998) comment on the fact that the magnitude of the shift in the case of acetylacetone ($\lambda_{max.}$ in EtOH = 273 mμ) amounts to 9, 21, 23, and 7 mμ on chelation with cobalt, nickel, copper, and zinc, respectively, and so follows the Irving–Williams order of stabilities: this might be expected if the extent of wave-length displacement indicated the degree of polarisation or deformation of the ligand. Similar regularities have been observed in the absorption spectra of metal complexes of 8-hydroxyquinoline-5-sulphonic acid (Marsh, *loc. cit.*), but a comparative study of other ligands (cf. *inter alia*, phthiocol; Geyer and Smith, *J. Amer. Chem. Soc.*, 1941, **63**, 3071) suggests that any oversimplified treatment of absorption spectra may be misleading, especially when chelation modifies the electron levels of the central metal ion (cf. Irving and Williams, *Analyst*, *loc. cit.*).

*Validity of Mellor and Maley's Order and Similar Empirical Sequences.*—Reference to the extensive data presented in Tables 1 and 2 shows that the empirical stability order noted by Mellor and Maley has only a very limited validity, for it does not remain the same when the ligand is changed. Thus, the order Mn < Fe < Cd < Co < Zn < Ni < Cu, valid for (almost) all amino-acids, fails for 8-hydroxyquinoline, where the position of iron and cadmium must be interchanged. With nitroacetic acid and diethylenetriamine, cadmium and cobalt are out of place; with salicylaldehyde, nitriloacetic acid, 8-hydroxquinoline-5-sulphonic acid, and histidine, cobalt and zinc exchange places; and with riboflavin (X) and folic acid (XI) no less than three pairs of metals must be interchanged to restore a

TABLE 2. *Successive stability constants of transition-metal complexes.*

| | Mn | Fe | Co | Ni | Cu | Zn |
|---|---|---|---|---|---|---|
| *Ammonia.*[1, 3] | | | | | | |
| log $K_1$ ..... | — | — | 2·11 | 2·79 [2] | 4·15 | 2·37 |
| log $K_2$ ..... | — | — | 1·63 | 2·24 | 3·50 | 2·44 |
| log $K_3$ ..... | — | — | 1·05 | 1·73 | 2·89 | 2·50 |
| log $K_4$ ..... | — | — | 0·76 | 1·19 | 2·13 | 2·15 |
| log $K_5$ ..... | — | — | 0·18 | 0·75 | −0·52 | — |
| log $K_6$ ..... | — | — | −0·62 | 0·03 | — | — |
| *Pyridine.*[4] | | | | | | |
| $(N/Z \log K + 1{\cdot}74$ | (0·1) | 0·6 | 1·1 | 1·7 | 3·2 | 1 9 |
| *Triethanolamine.*[5] | | | | | | |
| log $K_1$ ..... | — | — | 1·73 | — | 4·23 | 2·00 |
| *Ethylenediamine.*[6] | | | | | | |
| log $K_1$ ..... | 2·73 | 4·28 | 5·89 | 7·52 | 10·55 | 5·71 |
| log $K_2$ ..... | 2·06 | 3·25 | 4·83 | 6·28 | 9·05 | 4·66 |
| log $K_3$ ..... | 0·88 | 1·99 | 3·10 | 4·26 | −1·0 [7] | 1·72 |
| *Propylenediamine.*[8] | | | | | | |
| log $K_1$ ..... | — | — | — | 7·41 | 10·58 | 5·89 |
| log $K_2$ ..... | — | — | — | 6·30 | 9·08 | 4·98 |
| log $K_3$ ..... | — | — | — | 4·29 | — | 1·70 |
| *NN'-Dimethylethylenediamine.*[9] | | | | | | |
| log $K_1$ ..... | — | — | — | 6·67 | 9·69 | — |
| log $K_2$ ..... | — | — | — | 3·85 | 6·63 | — |
| 1 : 3-*Diaminopropane.*[10] | | | | | | |
| log $K_1$ ..... | — | — | — | — | 9·77 | — |
| log $K_2$ ..... | — | — | — | — | 7·17 | — |
| 1 : 3-*Diaminopropane-2-ammonium ion,* $(NH_2{\cdot}CH_2)_2CH{\cdot}NH_3^+$ (*Hptn*$^+$).[11] | | | | | | |
| log $K_1$ ..... | — | — | 4·1 | 6·0 | 8·8 | 4·25 |
| *Histidine.*[12] | | | | | | |
| log $K_1$ ..... | 4·23 | — | 7·52 [13] | — | 10·56 | 7·14 |
| log $K_2$ ..... | 3·51 | — | 6·34 | — | 7·77 | 5·74 |
| 1 : 2 : 3-*Triaminopropane.*[11] | | | | | | |
| log $K_1$ ..... | — | — | 6·8 | 9·3 | 11·1 | 6·75 |
| log $K_2$ ..... | — | — | — | — | 9·0 | — |
| *Diethylenetriamine.*[14] | | | | | | |
| log $K_1$ ..... | — | — | 8·1 | 10·7 | 16·0 [16] | 8·90 |
| log $K_2$ ..... | — | — | 6·0 | 8·25 | 5·3 | 5·5 |
| *Triethylenetetramine ion,* $NH_2{\cdot}C_2H_4{\cdot}NH{\cdot}C_2H_4{\cdot}NH{\cdot}C_2H_4{\cdot}NH_3^+$ (*Htrien*$^+$).[15] | | | | | | |
| log $K_1$ ..... | — | — | 6·8 | 8·9 | 14·0 | 7·3 |
| *Triaminoethylamine.*[17] | | | | | | |
| log $K_1$ ..... | 5·8 | 8·8 | 12·8 | 14·8 | 18·8 | 14·65 |
| *Triethylenetetramine.*[15] | | | | | | |
| log $K_1$ ..... | 4·9 | 7·8 | 11·0 | 14·0 | 20·4 | 12·1 |
| *β-Alanine.*[18, 19] | | | | | | |
| log $K_1$ ..... | — | — | — | 4·63 | 7·13 | — |
| log $K_2$ ..... | — | — | — | 3·40 | 5·47 | — |
| log $\beta_2$ ..... | — | — | ~7 [21] | 8·03 | 12·6 [20] | ~4 [21] |
| *Sarcosine.*[22] | | | | | | |
| log $K_1$ ..... | — | — | — | 4·96 | 7·32 | 4·12 |
| log $K_2$ ..... | — | — | — | 3·68 | 2·84 | 2·96 |
| DL-*Valine.*[23] | | | | | | |
| log $K_1$ ..... | 2·84 | — | 4·57 | — | 7·93 | 5·00 |
| log $K_2$ ..... | 2·72 | — | 3·67 | — | 6·52 | 4·10 |
| log $\beta_2$ ..... | 5·56 | 6·8 [21] | 8·6 [21] | — | 15·1 [21] | 9·10 |
| *Leucine.*[23] | | | | | | |
| log $K_1$ ..... | 2·78 | — | 4·55 | 7·89 | 4·92 | — |
| log $K_2$ ..... | 2·67 | — | 3·71 | 6·45 | 4·01 | — |
| *Norleucine.*[21] | | | | | | |
| log $\beta_2$ ..... | ~5 | 8·6 | 9·4 | 11·1 | 15·5 | 10·4 |
| *Phenylalanine.*[21] | | | | | | |
| log $\beta_2$ ..... | — | 6·3 | 7·9 | — | 14·9 | — |
| *Asparagine.*[21, 24] | | | | | | |
| log $\beta_2$ ..... | ~4·5 | 6·5 | 8·4 | 10·6 | 14·9 | 8·7 |
| *Serine.*[21] | | | | | | |
| log $\beta_2$ ..... | — | 7·0 | 8·0 | — | 14·6 | — |
| *Methionine.*[21] | | | | | | |
| log $\beta_2$ ..... | — | 6·7 | 7·9 | — | 14·7 | — |

TABLE 2. (*Continued.*)

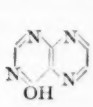
| | Mn | Fe | Co | Ni | Cu | Zn |
|---|---|---|---|---|---|---|
| *Proline.*[21] | | | | | | |
| log $\beta_2$ | ~5·5 | 8·3 | 9·3 | 11·3 | 16·8 | 10·2 |
| *Tryptophan.*[21] | | | | | | |
| log $\beta_2$ | ~5 | 7·6 | 8·5 | 10·2 | 15·9 | 9·3 |
| *Taurine.*[21] | | | | | | |
| log $\beta_2$ | — | 0 | ~4 | — | ~8 | — |
| *Glycylglycine.*[52] | | | | | | |
| log $K_1$ | 2·15 | — | 3·49 | 4·49 | 6·04 | 3·80 |
| log $K_2$ | — | — | 2·39 | 3·42 | 5·62 | 2·77 |
| *Nitroacetic acid.*[26] | | | | | | |
| log $K_1$ | — | — | 0·00 | 0·06 | 0·44 | 0·03 |
| *Nitriloacetic acid.*[27] | | | | | | |
| log $K_1$ | 7·44 | 8·84 | 10·61 | 11·26 | 12·68 | 10·45 |
| *Ethylenediaminetetra-acetic acid.*[28] | | | | | | |
| log $K_1$ | 13·47 | 14·22 | 16·10 | 18·45 | 18·38 | 16·15 |
| 2 : 2′-*Dipyridyl.* | | | | | | |
| log $K_1$ | — | 4·20[29] | — | — | — | — |
| log $K_2$ | — | <5 | — | — | — | — |
| log $K_3$ | — | >7·3 | — | — | — | — |
| log $\beta_3$ | — | 16·53 | — | — | 17·85[30] | — |
| 1 : 10-*Phenanthroline.*[34] | | | | | | |
| log $K_1$ | — | 5·9[31] | — | — | — | 6·43[33] |
| log $K_2$ | — | — | — | — | — | 5·72 |
| log $K_3$ | — | — | — | — | — | 4·84 |
| log $\beta_3$ | — | 21·3[32] | — | — | — | 17·0 |
| *Acetylacetone.*[35] | | | | | | |
| log $K_1$ | — | — | 6·30 | 6·82 | — | — |
| log $K_2$ | — | — | 4·88 | 5·20 | — | — |
| *Tropolone.*[49] | | | | | | |
| log $K_1$ | — | — | 7·04 | 7·61 | very large | 7·48 |
| log $K_2$ | — | — | 5·71 | 6·03 | 7·83 | 6·29 |
| *Salicylaldehyde.*[36] | | | | | | |
| log $K_1$ | 3·73 | 4·22 | 4·67 | 5·22 | 7·40 | 4·50 |
| log $K_2$ | 3·06 | 3·40 | 3·63 | 3·97 | 5·91 | 3·60 |
| *Salicylaldehydesulphonic acid.*[37] | | | | | | |
| log $K_1$ | — | — | 3·42 | 3·79 | 5·35 | 3·00 |
| log $K_2$ | — | — | ~2·2 | 2·77 | 3·92 | ~2·4 |
| 8-*Hydroxyquinoline.*[38] | | | | | | |
| log $K_1$ | — | 9·83 | 10·85 | 11·65 | 15·0 | 10·91 |
| log $K_2$ | — | 9·01 | 9·70 | 10·35 | 14·0 | 9·90 |
| log $K_1$[39] | 6·8 | 8·0 | 9·1 | 9·85 | 12·2 | too insol. |
| 8-*Hydroxyquinoline-5-sulphonic acid.*[40] | | | | | | |
| log $K_1$ | — | — | 9·25 | — | 11·5 | 8·70 |
| log $K_2$ | — | — | 7·45 | — | 10·7 | 7·20 |
| 4-*Hydroxypteridine* (IX).[41] | | | | | | |
| log $K_1$ | 2·35 | 3·40 | 3·84 | 4·36 | 4·82 | 3·41 |
| log $K_2$ | 2·12 | 2·70 | 2·81 | 3·5 | 4·72 | pptn. |
| *Riboflavin* (X).[42] | | | | | | |
| log $K_1$ | 3·44 | 7·12 | 3·88 | 4·11 | 6·62 | 5·58 |
| *Folic acid* (XI).[41] | | | | | | |
| log $\beta$ | 6 | 7·93 | 8·12 | 9·00 | 7·82 | 7·5 |
| *Cyanide ion.*[43] | | | | | | |
| log $K_1$ | — | 2? | 4·9 | 4·7 | 8? | 6·5 |
| *Hydroxide ion.*[44] | | | | | | |
| log $K_1$ | 2·83 | — | 3·6 | 3·8 | 7·8 | 4·5 |
| *Sulphate ion,*[45] | | | | | | |
| log $K_1$ | 2·28 | — | 2·47 | 2·40 | 2·3[48] | 2·40 |
| *Thiosulphate ion.*[45] | | | | | | |
| log $K_1$ | 1·95 | — | 2·05 | 2·06 | — | 2·40 |
| *Oxalic acid.*[46] | | | | | | |
| log $K_1$ | 3·89 | — | 4·70 | 5·30 | 6·16[47] | 4·89 |
| *Malonic acid.*[46] | | | | | | |
| log $K_1$ | 3·29 | — | 3·72 | 4·01 | 5·75[47] | 3·68 |

TABLE 2. (*Continued.*)

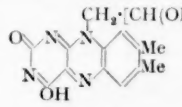
| | Mn | Fe | Co | Ni | Cu | Zn |
|---|---|---|---|---|---|---|
| *Succinic acid.*[47] | | | | | | |
| $\log K_1$ ..... | — | — | — | — | 3·33 | 2·48 |
| *Glutaric acid.*[47] | | | | | | |
| $\log K_1$ ..... | — | — | — | — | 3·16 | 2·30 |

[1] All values valid for 2M-$NH_4NO_3$ at 30°; Bjerrum, *op. cit.* For copper–*n*-butylamine complexes, see *idem*, *Acta Chem. Scand.*, 1950, **4**, 997. [2] Calvin (unpublished work quoted by Frank and Evans, *J. Chem. Phys.*, 1945, **13**, 507) reports $\log \beta_6 = 9{\cdot}13$ (23°) and 8·81 (30°). [3] For nickel–methylamine complexes Calvin (*loc. cit.*) reports $\log \beta_6 = 8{\cdot}64$ (15°) and 9·12 (35°). [4] Bjerrum's values [*Chem. Reviews*, 1950, **46**, 381 (Table 4)] are quoted. Measurements for Cu at 25° in 0·5M-Py,$HNO_3$ gave $\log K_1 = 2{\cdot}41$, $\log K_2 = 1{\cdot}88$, $\log K_3 = 1{\cdot}14$, and $\log K_4 = 0{\cdot}60$, whence $\log \beta_4 = 6{\cdot}03$ (Bjerrum and Nielsen, *Acta Chem. Scand.*, 1948, **2**, 297). Bruehlman and Verhoek (*J. Amer. Chem. Soc.*, 1948, **70**, 1401) give slightly higher values for 0·5M-$KNO_3$ at 25°, leading to $\log \beta_4 = 6{\cdot}54$. For Cu and γ-picoline complexes (*idem*, *ibid.*) $\log \beta_4 = 7{\cdot}74$ at 25°. [5] Valid for 0·5N-salt at 25° (Bjerrum, *Nord. Kem.*, Lund, 1947, p. 227). [6] All values valid for N-KCl at 30°. Data for Mn, Fe, and Co from Bjerrum, *op. cit.*, p. 293, and for Ni, Cu, and Zn from Carlson and McReynolds (*J. Amer. Chem. Soc.*, 1945, **67**, 1334). Additional data for Ni (Bjerrum, *op. cit.*), Cu (Bjerrum and Nielsen, *loc. cit.*), Zn (Bjerrum and Andersen, *Kgl. Danske Videnskab. Selsk.*, 1945, **22**, 3). [7] In N-$KNO_3$ at 25° (Bjerrum and Nielsen, *loc. cit.*). [8] All values valid for 30° (Carlson and McReynolds, *loc. cit.*); Ni and Zn in 0·5M-KCl, Cu in 0·5M-$KNO_3$. Laitinen, Onstott, Bailar, and Swann (*J. Amer. Chem. Soc.*, 1949, **71**, 1550) obtained $\log \beta_2 = 20{\cdot}17$ by polarography in 0·1M-$KNO_3$ at 25°. [9] Irving and Griffiths, in preparation. [10] Irving, Williams, Ferrett, and Williams (in prepn.) by polarography found $\log \beta_2 = 16{\cdot}67$ at 25°. [11] Valid for 0·1M-KCl at 20° (Prue and Schwarzenbach, *Helv. Chim. Acta*, 1950, **33**, 995). [12] Data for 25° by Maley and Mellor (*Nature*, 1950, **165**, 453) and Mellor and Maley (*Austral. J. Sci. Res.*, 1949, **2**, 579). [13] Calculation from measurements by other workers gives $\log \beta_2 = 11{\cdot}96$ (cf. Mellor and Maley, *loc. cit.*). However, Albert (*Biochem. J.*, 1952, **50**, 690) comments on irregular behaviour observed when titrating histidine with either cobalt or copper; his values of $\log \beta_2$ at 20° are 9·3 (Fe), 15·9 (Ni), and 12·0 (Zn), with $\log K_1 < 4$ for Mn. [14] Valid for 0·1N-KCl at 20° (Prue and Schwarzenbach, *loc. cit.*, p. 985). In 1·00M-$KNO_3$ + KCl the value $\log K_1 = 16{\cdot}11$, $\log K_2 = 3$—6 at 30° and $\log K_1 = 15{\cdot}63$ at 40° have been reported for Cu, and $\log K_1 = 10{\cdot}81$ (30°) and 10·54 (40°), $\log K_2 = 8{\cdot}14$ (30°) and 7·83 (40°) for Ni by Jonassen, LeBlanc, Meibohm, and Rogan (*J. Amer. Chem. Soc.*, 1950, **72**, 4968). [15] Valid for 0·1N-KCl at 20°(Schwarzenbach, *Helv. Chim. Acta*, 1950, **33**, 974). In M-$KNO_3$ the values $\log K_1 = 14{\cdot}3$ (30°) and 14·0 (40°) for Ni, and 20·6 (30°) and 20·1 (40°) for Cu complexes of triethylenetetramine have been reported by Jonassen and Meibohm (*loc. cit.*). For Ni, $\log K_2 = 5{\cdot}6$ (30°) and 5·4 (40°). [16] The value $\log \beta_2 = 20{\cdot}85$ at 25° in 0·1N-KCl has been obtained polarographically. [17] Valid for 0·1N-KCl at 20°; Prue and Schwarzenbach (*loc. cit.*, p. 963; Ackermann and Schwarzenbach, *Helv. Chim. Acta*, 1949, **32**, 1543). [18] Data for glycine and α-alanine are given in Table 1. [19] Glass-electrode measurements at 20° (Irving, Williams, Ferrett, and Williams, *loc. cit.*). [20] For Cu, Albert reports $\log \beta_2 = 12{\cdot}9$ (*Biochem. J.*, 1950, **47**, 531), and we find 12·7 (8) by polarography (Irving *et al.*, *loc. cit.*). [21] Albert (*Biochem. J.*, 1950, **47**, 531). [22] Unpublished observation. [23] Data for 25° by Maley and Mellor (cf. ref. 12). [24] For copper and aspartic acid, Li and Doody (*J. Amer. Chem. Soc.*, 1950, **72**, 1891) report $\log \beta_2 = 15{\cdot}20$ by polarography at 25° ($\mu = 1{\cdot}0$) but Albert [20] comments on certain complications, reporting $\log \beta_2$ as 8·5 (Fe), 10·7 (Co), 12·7 (Ni), and 10·4 (Zn), with $\log K_1 = 4{\cdot}0$ for Mn. [25] Data for 25° (Monk, *Trans. Faraday Soc.*, 1951, **47**, 297). [26] Pedersen (*Acta Chem. Scand.*, 1949, **3**, 676). [27] Valid for 0·1N-KCl at 20° (Schwarzenbach and Freitag, *Helv. Chim. Acta*, 1951, **34**, 1492). By polarography $\log K_1$ (Zn) = 10·35 at $\mu = 0{\cdot}2$ (Koryta and Kössler, *Coll. Trav. chim. Tchecosl.*, 1950, **15**, 241). [28] Valid for 0·1N-KCl at 20° (Schwarzenbach and Freitag, *loc. cit.*). Other values [27] for Fe, Cu, and Zn are 14·4(5), 18·8(6), and 16·5(8), respectively. [29] Data for 35° (Baxendale and George, *Trans. Faraday Soc.*, 1950, **46**, 55, 736); this includes values for other temperatures. Krumholtz (*J. Amer. Chem. Soc.*, 1945, **71**, 3654) reports $\log K_1 = 4{\cdot}36$. [30] Polarographic measurements in 0·1M-$KNO_3$ at 25° (Onstott and Laitinen, *ibid.*, 1950, **72**, 4724). [31] Data for 25° by Kolthoff, Leussing, and Lee (*ibid.*, p. 2173). [32] Valid for 25° (Lee, Kolthoff, and Leussing, *ibid.*, 1948, **70**, 2348). [33] Valid for 25° (*idem*, *ibid.*, 1951, **73**, 390). [34] Other less reliable values for complexes of iron with dipyridyl and phenanthroline are quoted in refs. 29—33. For iron and 2-methylphenanthroline (Irving, Cabell, and Mellor, in preparation) $\log K_1 = 4{\cdot}2$, $\log K_2 = 3{\cdot}7$, and $\log K_3 = 2{\cdot}9$. [35] Measured in 50% dioxan–water mixtures at 25° (Mellor and Maley, *Austral. J. Sci. Res.*, 1949, **2**, 92). [36] Valid for 50% dioxan–water at 25° (*idem*, *ibid.*; *Nature*, 1948, **161**, 436). [37] Data for 25° by Calvin and Melchior (*J. Amer. Chem. Soc.*, 1948, **70**, 3270). For Cu at 40°, $\log K_1 = 5{\cdot}64$ and $\log K_2 = 4{\cdot}15$. The stability constants of a large number of complexes of Cu with substituted *o*-hydroxy-benz- and -naphthaldehydes are given by Calvin and Wilson (*ibid.*, 1945, **67**, 2003). [38] Valid for 70% dioxan–water at 25° (cf. ref. 35). [39] Values obtained in water, presumably at low $\bar{n}$ values, by Albert (*Proc. Biochem. Soc.*, 1950, **47**, xxvii). [40] Data for 25° by Mellor and Maley (*Austral. J. Sci. Res.*, 1949, **2**, 579). [41] Albert (*Proc. Biochem. Soc.*, 1950, **46**, ix; and private communication). [42] Albert (ref. 39) and personal communication). [43] Bjerrum's values for (*N*/*Z*) $\log K + 1{\cdot}74$ are quoted from ref. 4, Table 4. [44] Calculated from hydrolysis measurements at 100° by Kullgren (*Z. phys. Chem.*, 1913, **85**, 466). [45] Denny and Monk (*Trans. Faraday Soc.*, 1951, **47**, 992, and refs. therein). [46] Monk (*ibid.*, p. 297. [47] Peacock and James (*J.*, 1951, 2233). This paper includes stability constants for copper complexes of many other aliphatic acids. [48] Fronaeus (*Acta Chem. Scand.*, 1950, **4**, 72) gives values for $K_1$, $K_2$, and $K_3$. [49] Fernelius, Bryant, and Douglas (*Nature*, 1952, **170**, 247). Valid for 50% dioxan–water at 30°.

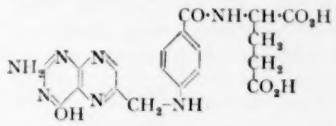
regularly increasing sequence of stability constants. Further examples of changes in the relative stability of iron, zinc, and cadmium complexes are detailed in Table 4.



(IX)



(X)



(XI)

From a consideration of the stability constants of a number of metals with glycine, alanine, glycylglycine, and several carboxylic acids, Monk (*Trans. Faraday Soc.*, 1951, **47**, 297) concluded that "the tendency to form complexes is in the order Cu > Ni > Zn > Pb ≈ Co > Mn > Mg > Ca > Sr > Ba, . . . although there are many gaps to fill in to see if this is universally true for all organic acids." This extended sequence has, however, little generality and it fails with, *e.g.*, the phenolic ligand salicylaldehyde, for which the order is Cu > Ni > Pb > Co > Zn > Mg ≈ Mn (points of divergency are underlined), with nitriloacetic acid (Cu > Pb > Ni > Co > Zn > Mn > Ca > Mg > Sr > Ba), ethylenediaminetetra-acetic acid (Ni > Cu > Pb > Zn ≈ Co > Mn > Ca > Mg ≈ Sr > Ba) and nitroacetic acid (p. 3196), while all the evidence against an invariable order Ni > Zn > Co presented above in criticism of Mellor and Maley's thesis is equally applicable here. Though the stability of alkaline-earth complexes has been fully discussed by one of us elsewhere (Williams, *loc. cit.*), it should be emphasised that the "natural" sequence Mg > Ca > Sr > Ba does not hold for many complexones or indeed for all the ligands to which Monk refers (*e.g.*, glycylglycine and malic acid).

Although it is apparent that the empirical stability orders of Mellor and Maley, or of Monk, and of other authors, do not hold for all the ligands cited in Tables 1 and 2 and are often at variance with stability orders established kinetically (cf. p. 3197), yet the Irving–Williams order appears to hold almost without exception. We shall therefore proceed to show how theoretical considerations lead to just this stability sequence, and indeed predict certain points of divergence such as the abnormally high stability of certain ferrous complexes (*e.g.*, those with dipyridyl and phenanthroline, but not with ethylenediamine) and the anomalous low stability of certain copper complexes (*e.g.*, those of ethylenediaminetetra-acetic acid, triaminopropane, and folic acid) which have been observed experimentally.

*Factors controlling the Stability of Metal Complexes.*—No simple picture of interaction between ligand and metal ion in terms of purely coulombic forces will explain why, *e.g.*, no ammines of $Na^+$ exist while those of $Cu^{++}$ and $Ag^+$ are stable in aqueous solution, for the dipole moment of water is larger than that of ammonia. However, ammonia ($\alpha = 2{\cdot}4 \times 10^{-24}$) is more polarisable than water ($\alpha = 1{\cdot}5 \times 10^{-24}$), and by considering ion–dipole and induced dipole interactions, Van Arkel and Boer (*Rec. Trav. chim.*, 1928, **47**, 593) were able to show that the tendency towards ammine formation should increase with decreasing radius and increasing deforming power of the cationic partner. Table 3 shows that the ionic radii of bivalent ions of the first transition series decrease slightly but regularly from manganese to copper and increase again at zinc. The heat of hydration of these ions follows the same sequence (Table 3), so the stability of aquo-complexes of bivalent transition metals follows the same order as that found for other ligands reported above. But if this sequence is extended to include other bivalent ions, the order of decreasing ionic radius will not necessarily coincide with the order of increasing complex stability. For instance, the ions $Mg^{++}$ and $Ca^{++}$ of the alkaline-earth metals have radii respectively smaller and greater than any in the first transition series from manganese to copper, yet their complexes with any given ligand are invariably less stable than those formed by the bivalent transition metal ions. Indeed, Fig. 3 shows that, while the heats of hydration of bivalent ions of the alkaline-earth metals lie on a smooth curve when plotted against the reciprocal of their ionic radii, those of the transition metals deviate in the direction of higher stability and to an extent which closely follows the Irving–Williams

order. This disposes of any naive suggestion that complex stability in this series is governed by purely electrostatic forces. A similar effect can be observed among hydroxy-complexes. Davies (*J.*, 1951, 1256) has shown that if complexes between cations and hydroxyl ions were purely electrostatic in character, a simple relation would exist between their dissociation constants, $K$, and the radius, $r$, of the unhydrated ion and its

TABLE 3. *Bivalent ions of the first transition series.*

| | Mg | Mn | Fe | Co | Ni | Cu | Zn | Cd | Ca |
|---|---|---|---|---|---|---|---|---|---|
| Radius, Å ..... | 0·66 | 0·78 | 0·76 | 0·74 | 0·73 | 0·72 | 0·72 | 0·96 | 0·99 |
| $E_2$, kcal. ..... | 525·7 | 534·7 | 558·6 | 586 | 599 | 648·6 | 633·5 | 599·9 | 417·5 |
| $H$, kcal. ..... | 464·0 | 444·7 | 467·9 | 497 | 507 | 507·2 | 491·5 | 436·5 | 381·9 |

The data are taken from Brewer, Bromley, Gilles, and Lefgren (National Nuclear Energy Series, Division IV–19B, McGraw Hill, 1950, p. 154); $E_2$ refers to the total ionisation potential at 25° for the process M (gas) ⟶ $M^{++}$ (gas) + $2e$. The third row gives values for the heat of hydration of gaseous ions at 25° corresponding to the equation $M^{++}$ (gas) + aq. ⟶ M $(aq.)^{++}$. Using the method of Kordes (*Z. phys. Chem.*, 1939, **43**, 213), we calculate a radius of 0·71 Å for $Cu^{++}$.

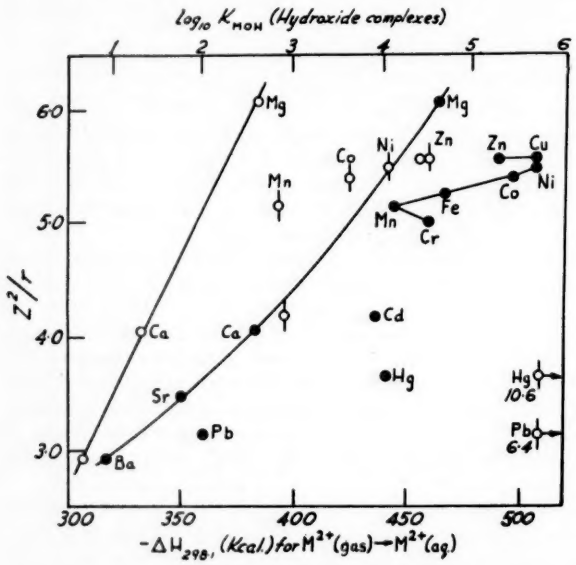



FIG. 3. *Hydroxy- and aquo-complexes of bivalent ions.*

○ Hydroxide complexes.
◌ Values calc. from Kullgren's data, ref. 60.
● Heats of hydration.

valency, $z$. For the ions $Li^+$, $Na^+$, $Mg^{++}$, $Ca^{++}$, $Ba^{++}$, and $La^{+++}$ this takes the form $pK = 0{\cdot}607z^2/r - 1{\cdot}156$. Fig. 3 shows part of this plot for the ions $Mg^{++}$, $Ca^{++}$, and $Ba^{++}$, and it is at once obvious that hydroxy-complexes of the transition metals (and of other bivalent ions such as $Pb^{++}$ and $Hg^{++}$) are much more stable than can be accounted for by purely electrostatic forces of attraction. A similar conclusion would be drawn from the plot of the stability of metal ammines in aqueous solution, those of the transition metals being very much more stable than could have been expected from the measured values for $Mg^{++}$ and $Ca^{++}$ for which $\log \beta_6 = -3{\cdot}3$ and $-5{\cdot}7$ respectively (Bjerrum, *op. cit.*, p. 191; cf. Table 2). In this case it must not be overlooked that stabilities are measured relatively to those of aqueous complexes. But since these stabilities increase regularly along the series manganese to copper (cf. Table 3) it follows that there is a similar monotonic rise in absolute stability from manganese to copper in the case of the ammine complexes, since the increments in relative stability on replacing water by ammonia molecules (cf. Fig. 1) increase in the same order.

That replacement of water by a more polarisable ligand should lead to an enhanced stability is not surprising. That the *increments* in stability should increase monotonically along the Irving–Williams series (but not necessarily along a series including other bivalent ions even when arranged in order of diminishing radius) can only mean that some

additional stabilising factor is in operation which increases in extent as we move along the series : this must be the tendency towards the formation of a covalent bond between metal and ligand. This point is brought out more clearly in Fig. 4, which shows that, while the stability sequence follows the Irving–Williams order for all the ligands represented, the stability increment from metal to metal is greatest for nitrogen-type ligands (*e.g.*, ethylenediamine), less for nitrogen–oxygen-type ligands (*e.g.*, glycine), and still less for oxygen–oxygen-type ligands (*e.g.*, salicylaldehyde and oxalic acid). Indeed, the difference between the " slopes " of the stability graphs leads to the important result that the order of stability ethylenediamine > amino-acids > salicylaldehyde, which holds for the elements cobalt to zinc, is actually reversed for manganese. Although an invariable order of stability may well be possible for different ligands acting with a limited series of metals, yet an invariable order for different metals forming complexes with an arbitrary sequence of ligands is highly improbable. Furthermore, the more electropositive the co-ordinating atom of the ligand, the greater the stability increment from metal to metal; this emphasises the significance of covalent bonding in determining the stability of complexes.

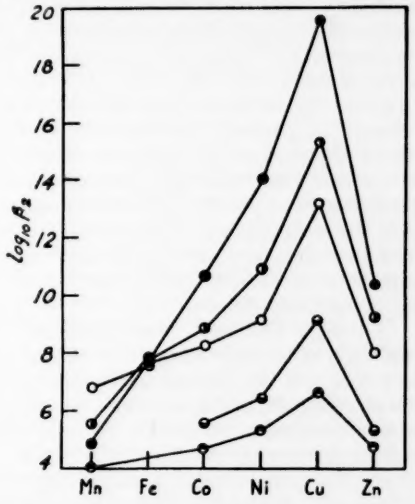



FIG. 4. *Transition-metal complexes with various types of ligand.*

○ Salicylaldehyde.
◑ Glycine.
● Ethylenediamine.
◒ Salicylaldehydesulphonic acid.
◓ Oxalic acid (values of $\log_{10} \beta_1$).

Now any more elaborate picture of co-ordination must take into account the available electronic levels of the (acceptor) metal ion and the electron availability of the (donor) ligand. Thus, Walsh (*Proc. Roy. Soc.*, 1951, **207**, *A*, 13; cf. *J.*, 1948, 398) relates the strength of the co-ordinate link (among other factors) to the product $\chi_L\chi_M$, where $\chi_L$ and $\chi_M$ are the effective electronegativities of the metal and ligand respectively. As a measure of the electron-affinity of the acceptor cation, we may adopt the second ionisation potential corresponding to the process $M(gas) \longrightarrow M^{2+}(gas) + 2e$. This refers to the free atom and reflects the ground-state energy levels of the electrons. The strength of the co-ordinate link may thus be related to the loss of potential energy when electrons are donated from the high-energy levels of the ligand to the lower-energy levels of the metal ion. Such a picture is, of course, oversimplified, for on co-ordination both sets of levels are mutually adjusted and the effect of bond polarity must be taken into account (cf. Walsh, *loc. cit.*). Nevertheless, the clear correlation between ionisation potential and complex stability must not be underestimated, and it is of the greatest significance that, as Table 3 shows, the second ionisation potential rises along the transition series to a maximum at copper and falls again at zinc. This correlation with the stability of transition-metal complexes was first pointed out by us in 1948 (*Nature*, **162**, 146) and has since been noted by Schwarzenbach, Ackermann, and Prue (*ibid.*, 1949, **163**, 723), and by Calvin and Melchior (*J. Amer. Chem. Soc.*, 1948, **70**, 3270) in connection with their measurements of complexes of salicylaldehyde-5-sulphonic acid with the four metals

copper, nickel, cobalt, and zinc, although in this case reference was made only to the second-stage ionisation process, $M^{+} \longrightarrow M^{++} + e$, which clearly has less fundamental significance.

In our picture of co-ordination, the electron donation from ligand to cation must bring about a reduction in its formal charge. This process is in fact that envisaged in Pauling's *postulate of the essential neutrality of atoms* (*J.*, 1948, 1461; Volume commemoratif Victor Henri, Liége, 1947, p. 1), but the use of the second ionisation potential ($M \longrightarrow M^{++}$) as a measure of the driving force of this process supplies a quantitative element which is absent from this theory. Indeed, in its present form, Pauling's theory fails to account even qualitatively for the order of stability of metal complexes. For, from considerations of the standard electrode potentials of the bivalent ions from $V^{2+}$ to $Zn^{2+}$ (which form a measure of the free-energy change in transference of metal from the solid lattice to hydrated ions in solution), and the stability of their respective metal lattices as indicated by his values for their metallic valencies, Pauling concludes (Volume commemoratif, *loc. cit.*) that the hydrated ions of $Fe^{++}$, $Co^{++}$, and $Ni^{++}$ "are associated with a special instability" and that there is "a much greater instability for the cupric and zinc ions which causes the electrode potential to be lowered by as much as 1·5 volts." This deduction conflicts with the experimental results (Table 3), which place the stability of the hydrates in the familiar order $Mn < Fe < Co < Ni < Cu > Zn$.

Even the additional assumptions (*idem*, *loc. cit.*) that maximum bond stability in the complex $ML_n$ is achieved when the number of available strong orbitals, $m$, is equal to $n$ (when unsynchronised resonance is permitted) while less stable structures result when $m < n$ (since only unsynchronised resonance is then possible), do not permit of the reliable prediction of any orders of relative stability for complexes of different transition metals with the same ligand. This is scarcely surprising, since the basic simplifying assumption that the electronegativities of all the transition metals are about 1·5 units necessarily ignores the important specific features of metal–ligand interaction which we know to be of paramount importance.

Although Pauling's theory does not predict the Irving–Williams order and cannot explain why it holds so extensively, we suggest that it is essentially a consequence of the fact that the two parameters which respectively serve as a guide to the magnitude of the electrostatic and covalent interactions, *viz.*, the reciprocal of the ionic radius, and the second ionisation potential, both increase monotonically throughout the series from manganese to copper. Thus, if water is replaced by a ligand of greater electron-donating power, the gain in stability will increase with the second ionisation potential of the metal concerned. If water is replaced by a ligand with a formal negative charge, the stability increment through purely electrostatic forces will increase as the radius of the cation decreases, *i.e.*, in the same order. Hence, in our limited sequence, provided there is any increase in interaction energy on replacement of water by some other ligand, there is bound to be a monotonic gain in stability in passing along the series from manganese to copper irrespective of the extent to which either or both of these factors may operate. For the same reason the stability order $Cu > Zn$ must always be true, in agreement with experience. But there is no such invariable relation to be expected between the stability of zinc complexes and those of the other transition metals, since zinc has a higher ionisation potential but a lower radius than, *e.g.*, nickel and cobalt. Orbital stabilisation, which generally increases the stability of copper complexes and sometimes those of ferrous iron, will be considered later (p. 3206).

Mellor and Maley (*loc. cit.*) naturally considered the significance of ionic radius and electronegativity in discussing their empirical order of stability which included elements such as Cd, Pd, Pb, Mg, etc., as well as members of the first transition series. Their failure to observe any clear correlation between complex stability and ionic radius or any other parameter such as electronegativity which might be related empirically to this magnitude) springs solely from the inclusion in their series of ions which perturb the dual monotonic sequences of ionic radius and ionisation potential which characterise the metals of the Irving–Williams sequence. If, for example, we were to include cadmium in our series, and note that the ionic radius of cadmium is greater than that of nickel although the

ionisation potentials are almost identical (Table 3), it is clear that the relative stabilities of cadmium and nickel complexes must depend upon the nature of the ligand, and no invariable order could be expected. Consider first the hydroxide complexes. For this ligand, $OH^-$, there is an increase both in formal charge and in electron-donating power, compared with water, so the order will be Ni > Cd. When water is replaced by the iodide ion, however, there is admittedly a slight increase in electron-donating power, but since the iodide ion is so much larger than a water molecule the decrease in electrostatic interaction due to the greater charge separation will be more significant with the smaller nickel ion, and since the gain in covalent interaction energy is much the same (ionisation potentials Ni ≅ Cd) the stability order becomes Cd > Ni. An obvious extension of this argument will show why all bivalent ions of large radius and high ionisation potential, *e.g.*, Pb, Hg, Pt, and Sn, should tend to form strong complexes with iodide, bromide, and chloride ion, whereas ions with large radius and low ionisation potentials, *e.g.*, Ba, Sr, and Ca, will not. With ions of moderately small radius and moderately high ionisation potential, changes of ligand produce changes in the relative significance of the two factors (electrostatic and covalent interaction) and no reliable prediction of an order of stability can be attempted save in the favourable case—exemplified by the bivalent ions of the first transition series from Mn to Cu—where the two factors invariably co-operate.

*Factors which may cause a Derangement of the Irving–Williams Order.*—The formation in solution of the most stable co-ordination compound which can be formed from a given hydrated ion and ligand molecules is attained by the interplay of various factors which can be roughly analysed as follows under three headings. (i) There is the tendency to pack as many ligands as possible around the central ion so as to obtain the maximum total interaction by way of the greatest number of individual interactions. This factor is limited by the " interference volume " of the ligand molecules compared with that of the water molecules which they must displace from around the central ion. (ii) The atomic electrons will tend to remain in their most stable ground state. This factor is often opposed by factor (iii), which is the tendency to make each individual interaction as strong as possible through the use of the strongest possible hybrid bonding orbitals.

Bjerrum (*op. cit.*, p. 58) gives great weight to the view that " in the main, metal ammine formation proceeds statistically " (cf. Burkin, *Quart. Reviews*, **1951**, **5**, 1). We would agree that a ligand would replace water statistically from its co-ordination positions round a cation in solution provided that (*a*) the interference volume of the ligand did not differ significantly from that of water, (*b*) the electrostatic repulsion between the new ligands did not differ significantly from that between water molecules, and (*c*) there was no change in orbital configuration at any stage during complex formation. Clearly, cases of strictly statistical addition and replacement of ligands must be rather exceptional. Consider, for example, the co-ordination of amines to nickel, zinc, and copper, respectively. In the case of nickel, addition of ammonia proceeds uniformly up to a co-ordination number $N = 6$, and magnetic data do not suggest any changes in the number of unpaired electrons throughout this process. The same is true for ethylenediamine and 1 : 10-phenanthroline which form tris-complexes, and the effect of complex formation is only to quench the orbital contribution and to reduce the total magnetic moment from ~3 to 2·83 Bohr magnetons (Russell, Cooper, and Vosburg, *J. Amer. Chem. Soc.*, **1943**, **65**, 1301). With zinc, however, only four molecules of ammonia can be co-ordinated and, as these are certainly not added statistically (cf. Table 2, and Bjerrum, *op. cit.*), it seems possible that they are replacing six water molecules, and in an irregular way. The zinc ion normally uses $4s4p^3$ tetrahedral orbitals and the high ionisation potential of the metal coupled with the electronegativity of nitrogen must favour, at some stage, the attachment of ammonia molecules through these hybrid bonds rather than the weaker attachment of water molecules: factor (ii) predominates here. Ethylenediamine has a smaller interference volume than ammonia (Irving, Williams, Ferrett, and Williams, *loc. cit.*), and two molecules co-ordinate readily and a third with markedly greater difficulty, while 1 : 10-phenanthroline molecules displace water to give a tris-complex of about the stability expected on statistical grounds from a knowledge of the stability of the 1 : 1 and 1 : 2 complexes (cf. Table 2). With ethylenediamine, and still more so with phenanthroline, factor (i)

appears to prevail—unless $4s4p^34d^2$ orbitals are called into play. In the case of copper the use of $dsp^2$ orbitals would favour four coplanar bonds, though there is the possibility of weaker interaction in the plane perpendicular to these (cf. Kuhn, *J. Chem. Phys.*, 1948, **16**, 727). Possibly $4s4p^24d$ hybridisation is used, the ground state of the $Cu^{2+}$ ion remaining completely unchanged on complex formation. But it is only with great reluctance that a fifth molecule of ammonia or a third molecule of ethylenediamine is co-ordinated (Table 2) so that factor (ii) is here of paramount importance.

In the absence of orbital stabilisation (factor iii) both the number and the kind of hybrid orbitals available for bonding are to a large extent determined independently of the nature of the ligand. This implies that both the maximum co-ordination number and the favoured stereochemistry will normally be independent of the nature of the ligand. Conformability with these restrictions, or exceptional behaviour, will be of equal importance when considering the validity of stability orders; behaviour of either type will be of significance in, *e.g.*, analytical chemistry. Of even greater theoretical and practical importance are those cases discussed in the next section, where factor (iii) dominates the others.

*Orbital Stabilisation.*—Since our stability order is largely independent of the nature of the ligand concerned, the observed correlation with the second ionisation potential may be taken as indicating that co-ordination has not altered the electronic ground states of the metal ions, or that any modifications are of secondary importance. That this is an over-simplification is shown immediately by the fact that the cupric ion utilises $dsp^2$ orbitals in all its complexes rather than the $sp^3$ orbitals expected from consideration of its ground state; the gain in bond energy more than compensates for the energy needed to promote the unpaired 3*d* electrons to a higher level (Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1948, p. 104). It is perhaps fortuitous that this orbital stabilisation occurs with an ion which would in any case form the strongest complexes of all the bivalent transition cations (see above) so that no derangement of stability order is caused. This is no longer the case with certain ferrous complexes where orbital stabilisation gives rise to complexes of abnormally high stability; and since the effect does not operate with its neighbours manganese or cobalt, or even with nickel and copper, a derangement of the " natural " order of stability appears.

Although, *e.g.*, ethylenediamine or triethylenetetramine gives paramagnetic and almost colourless complexes with ferrous iron, certain other nitrogen–nitrogen types of ligand such as 1 : 10-phenanthroline (VI) and 2 : 2′-dipyridyl (V) give complexes of unexpectedly high stability (Table 4) in which electronic rearrangement is revealed by the appearance of a high intensity absorption band in the visual region and the complete loss of paramagnetism which in the case of the aliphatic complexes corresponds to three unpaired 3*d* electrons. As in the case of the isoelectronic hexamminocobaltic complexes, the six atomic electrons of the ferrous ion have formed three shared pairs, leaving two 3*d* orbitals for use in strong octahedral $d^2sp^3$ hybrid bonds. The implications of such orbital stabilisation in analytical chemistry will be discussed elsewhere in connection with the " ferroin " and " cuproin " reactions (Irving, to be published shortly; cf. Irving and Williams, *loc. cit.*), but its effect in modifying or reversing an arbitrary order of stability can be seen in the data presented in Table 4 for certain complexes of zinc, cadmium, and iron, where the number of ligand molecules co-ordinated per atom of metal is shown in the second column and the arrangement within each of the three groups is that of increasing stability of the ferrous complexes. It will be obvious that no invariable " order of stability " can be laid down for these three metals (cf. p. 3197). Complexes of zinc are generally stronger than those of cadmium, but to no very marked extent; in some cases the difference in stability is negligible or even in the reverse order. For iron, on the other hand, the stability will be seen to increase relative to zinc or cadmium whenever additional resonance energy stabilisation is introduced through a ligand with an aromatic ring system (indicated by asterisks in Table 4) and in such circumstances the three metals may give complexes of closely similar stability while, consistently with the hypothesis that favourable electronic rearrangement is stabilising ferrous, but not zinc or cadmium complexes, the stability order is ultimately reversed to give Fe > Cd and Zn. There is some evidence from the

trend in stability constants here and with some nickel complexes that a measure of *d* orbital stabilisation takes place before there is any reason to suspect this from changes in magnetic moment. Since the hydrated ferrous ion is paramagnetic while the trisphenanthroline and dipyridyl complexes are diamagnetic, orbital stabilisation may have occurred concurrently with the chelation of the first, second, or third molecule of ligand (Williams, Thesis, Oxford, 1950; Irving, "Discussion on Co-ordination Chemistry," September 1950, Imperial Chemical Industries Limited, Report No. BRL/146). It is

TABLE 4. *Some complexes of zinc, iron, and cadmium.*

| Ligand | No. of molecules | log of | Zn | Fe | Cd | Refs.[1] |
|---|---|---|---|---|---|---|
| Ammonia | 2 | $K_1K_2$ | 4·43 | 1 | 4·47 | 2 |
| 4-Hydroxypteridine (IX) * | 1 | $K_1$ | 3·41 | 3·40 | 3·41 | 3 |
| Salicylaldehyde (as VII) * [4] | 1 | $K_1$ | 4·50 | 4·22 | 5·47 | 5 |
| Ethylenediamine | 1 | $K_1$ | 5·71 | 4·28 | 5·47 | 6, 7 |
| *o*-Phenanthroline (VI) * | 1 | $K_1$ | 6·50 | 5·90 | 6·6 | 8 |
| Riboflavin (X) * | 1 | $K_1$ | 5·58 | 7·12 | 4·72 | 10 |
| 8-Hydroxyquinoline (as VIII) * [11] | 1 | $K_1$ | 9 | 8·0 | 7·2 | 10 |
| Ammonia | 4 | $K_1K_2K_3K_4$ | 9·48 | 2 | 7·12 | 2 |
| Glycine | 2 | $K_1K_2$ | 9·3 | 4 | 8·1 | 12 |
| Tryptophan | 2 | $K_1K_2$ | 9·3 | 4 | 8·1 | 12 |
| Asparagine | 2 | $K_1K_2$ | 8·7 | 4 | 6·8 | 12 |
| Proline | 2 | $K_1K_2$ | 10·2 | 4 | 8·7 | 12 |
| Ethylenediamine | 2 | $K_1K_2$ | 10·34 | 7·53 | 10·02 | 6, 7 |
| Salicylaldehyde (as VII) * [4] | 2 | $K_1K_2$ | 8·10 | 7·62 | 7·76 | 5 |
| Triethylenetetramine (IV) | 1 | $K_1$ | 12·1 | 7·8 | 10·75 | 13, 14 |
| Folic acid (XI) * | 2 | $K_1K_2$ | 7·5 | 7·93 | 6·7 | 3 |
| Norleucine | 2 | $K_1K_2$ | 10·4 | 8·61 | 8·7 | 12 |
| 8-Hydroxyquinoline * [11] (as VIII) | 2 | $K_1K_2$ | 20·81 | 18·84 | — | — |
| Ethylenediamine | 3 | $K_1K_2K_3$ | 12·09 | 9·53 | 12·09 | 6, 7, 9 |
| 2 : 2′-Dipyridyl (V) * | 3 | $K_1K_2K_3$ | — | 16·5 | 10·5 | 15 |
| *o*-Phenanthroline (VI) * | 3 | $K_1K_2K_3$ | 17·0 | 21·5 | 15·2 | 9 |
| Ethylenediaminetetra-acetic acid | 1 | $K_1$ | 16·15 | 14·22 | 16·48 | 16 |

The asterisk * is used to call attention to ligands containing an aromatic ring system.

[1] References to data for zinc and iron complexes from Table 1 and 2. [2] Bjerrum (*op. cit.*). [3] Albert (*Proc. Biochem. Soc.*, 1950, **46**, ix). [4] Values measured in 50% dioxan : in water the values would be about 0·8 log *K* unit lower per molecule of ligand. [5] Mellor and Maley (*Nature*, 1948, **161**, 436). [6] Carlson and McReynolds (*J. Amer. Chem. Soc.*, 1945, **67**, 1334). [7] Bjerrum and Andersen (*Kgl. Dansk Videnskab. Selsk.*, 1945, **22**, 3). [8] Estimated from the value log $\beta_3 = 13{\cdot}2$ of ref. 9. [9] Douglas, Laitinen, and Bailar (*J. Amer. Chem. Soc.*, 1950, **72**, 2484). [10] Albert (*Proc. Biochem. Soc.*, 1950, **47**, xxvii). [11] Measured in 70% dioxan : values in water will be 1·5 —2·0 log *K* units lower per molecule of ligand. [12] *Idem* (*Biochem. J.*, 1950, **47**, 531). [13] Schwarzenbach (*Helv. Chim. Acta*, 1950, **33**, 974). [14] The value 13·9 has been obtained polarographically, ref. 9. [15] Baxendale and George (*Trans. Faraday Soc.*, 1950, **46**, 55, 736; Krumholtz, *J. Amer. Chem. Soc.*, 1949, **71**, 3654). [16] Schwarzenbach and Freitag (*Helv. Chim. Acta*, 1951, **34**, 1492).

hoped later to present results which will correlate paramagnetic susceptibility measurements with the degree of complex formation, not only for these ligands, but also for others such as 2-methyl-1 : 10-phenanthroline where weaker complexes are known to be formed as a consequence of steric hindrance (Irving, Cabell, and Mellor, *loc. cit.*) and for complex ligands of biological interest such as 4-hydroxypteridine, folic acid, and riboflavin, whose behaviour is somewhat exceptional in other respects.

*Steric Considerations.*—Steric interference between ligands arises from mutual repulsion and, apart from special features of ligand geometry, will be greater the greater the size of the ligand and the smaller the radius of the cation. Among the transition metals the radii of bivalent ions are much the same (0·78—0·71 Å) and the varying geometry of the ligand is of predominant importance. This will no longer be true when ions of very different size are considered as, *e.g.*, among the alkaline-earth metals (Williams, *J.*, 1952, 3770).

An estimate of the magnitude of steric hindrance can be made by calculating the free-energy change incurred when one ligand is replaced by another of similar type. Thus since log $K_1$(en) and log $K_1K_2(NH_3)$ are measures (in units of $4{\cdot}57T$ cal./mole) of the free-energy changes of the reactions

$$M^{++}(aq.) + en(aq.) = M(en)(aq.)^{++} + nH_2O$$

and

$$M^{++}(aq.) + 2NH_3(aq.) = M(NH_3)_2(aq.)^{++} + mH_2O$$

it follows that $\log K_1(\text{en})/K_1K_2(NH_3)_2$ is a similar measure of the free-energy change in the displacement reaction

$$M(NH_3)_2(aq.)^{++} + en(aq.) = M(en)(aq.)^{++} + 2NH_3(aq.) + (n - m)H_2O \quad . \quad (1)$$

Since the extent of hydration and thence the number of water molecules involved in such reactions cannot be determined unequivocally—although it will certainly vary from one ligand species to another—too much emphasis cannot be placed on the absolute values for the logarithmic differences quoted in Table 5 although it is possible to see how the free energy changes as the type and extent of chelation is altered. However, a comparison of reactions of type (1) for a number of different metals with the same pair of ligands should reveal features specific to these metals provided the degree of hydration (or more precisely the difference, $n - m$) remains the same throughout. It is permissible in this way to compare bivalent ions of the first transition series, for they are all of similar size and kind, and the degree of hydration should not vary greatly. But similar comparisons between ions of greatly different radii would be of doubtful validity.

TABLE 5.

(a) *Changes in free energy when one ligand replaces another.*

| Reaction represented by: | Co | Ni | Cu | Zn |
|---|---|---|---|---|
| $\log K_1(\text{en}) - \log K_1K_2(NH_3)$ | 2·15 | 2·49 | 2·90 | 0·90 |
| $\log K_2(\text{en}) - \log K_3K_4(NH_3)$ | 3·02 | 3·36 | 4·03 | 0·01 |
| $\log K_1(\text{Hptn}^+) - \log K_1K_2(NH_3)$ | 0·4 | 1·07 | 1·15 | −0·6 |
| $\log K_1(\text{Hptn}^+) - \log K_1(\text{en})$ | −1·8 | −1·5 | −1·8 | −1·5 |
| $\log K_1(\text{ptn}) - \log K_1K_2K_3(NH_3)$ | 2·0 | 2·5 | 0·6 | −0·6 |
| $\log K_1(\text{den}) - \log K_1(\text{ptn})$ | 1·3 | 1·4 | 4·9 | 2·15 |
| $\log K_1(\text{den}) - \log K_1K_2K_3(NH_3)$ | 3·3 | 3·9 | 5·5 | 1·6 |
| $\log K_1(\text{trien}) - \log K_1K_2K_3K_4(NH_3)$ | 5·45 | 6·05 | 7·7 | 2·65 |
| $\log K_1(\text{tren}) - \log K_1K_2K_3K_4(NH_3)$ | 7·25 | 6·85 | 6·1 | 5·2 |
| $\log K_1(\text{tren}) - \log K_1(\text{trien})$ | 1·8 | 0·8 | −1·6 | 2·55 |
| $\log K_1(\text{tren}) - \log K_1K_2(\text{en})$ | 2·08 | 1·0 | −0·83 | 4·29 |

(b) *Energy increments per atom of nitrogen co-ordinated when a polydentate ligand replaces ammonia in the co-ordination sphere.*

| | | | | |
|---|---|---|---|---|
| $\frac{1}{2}[\log K_1(\text{en})/K_1K_2(NH_3)]$ | 1·07 | 1·25 | 1·45 | 0·45 |
| $\frac{1}{3}[\log K_1(\text{den})/K_1K_2K_3(NH_3)]$ | 1·10 | 1·30 | 1·83 | 0·53 |
| $\frac{1}{4}[\log K_1(\text{trien})/\log K_1K_2K_3K_4(NH_3)]$ | 1·39 | 1·51 | 1·92 | 0·66 |
| $\frac{1}{4}[\log K_1(\text{tren})/\log K_1K_2K_3K_4(NH_3)]$ | 1·81 | 1·69 | 1·53 | 1·30 |

Values throughout are in units of $4{\cdot}57T$ cal./mole.

Values of $\log [K_1(\text{en})/K_1K_2(NH_3)]$ show that there is always a gain in stability when the monodentate ligand ethylenediamine replaces two molecules of ammonia. Moreover, the stability increments follow the Irving–Williams order Co < Ni < Cu > Zn. Values of $\log [K_2(\text{en})/K_3K_4(NH_3)]$ show that this is equally true for the replacement of the third and the fourth attached group. The much smaller gain in stability when one molecule of the charged bidentate ligand, $(NH_2{\cdot}CH_2)_2{\cdot}CH{\cdot}NH_3^+$(Hptn$^+$), replaces two molecules of ammonia, and the actual decrease in stability when Hptn$^+$ replaces "en" is due partly to the repulsion between the metal cation and the charged 'onium group (Schwarzenbach, "Discussion on Co-ordination Chemistry," *loc. cit.*; cf. *Angew. Chem.*, 1950, **50**, 74) and partly to the increased size of the chelate ring (Irving, Williams, Ferrett, and Williams, *loc. cit.*); differences in hydration may well be of importance here. Table 5 shows the notable gain in stability when two chelate groups are attached simultaneously through a tridentate group, the values again attaining their maximum with copper. Values of $\log K_1(\text{den})/K_1(\text{ptn})$ show that there is always a gain in stability on replacing triaminopropane (ptn) by an unbranched triamine (den) which can more readily adapt itself to the stereochemistry of the atom to which it is co-ordinated and which is especially well suited to the formation of three coplanar rings when chelating to an ion which uses planar $dsp^2$ orbitals. Among the metals listed in Table 5 this gain is especially marked in the case of copper, and conversely the use of ptn produces an abnormally weak copper complex in which it probably acts as a bidentate ligand (cf. Mann, *J.*, 1926, 2680).

Table 5 shows that the stability increment per atom of nitrogen co-ordinated when a

polydentate ring replaces an equivalent number of ammonia molecules increases in the order bidentate < tridentate < quadridentate, *i.e.*, in the order of increasing number of chelate rings simultaneously attached, and with the exception of tren in the familiar order Co < Ni < Cu > Zn. The exceptional behaviour of triaminoethylamine (tren) is most clearly shown in the values of log $K_1$(tren)/$K_1$(trien) which strikingly demonstrate the need for mutal compatibility between the geometry of the ligand and the stereochemistry favoured by the cation if maximum stability is to be attained. That the configuration of tren is particularly well adapted to complexing with metals favouring a tetrahedral disposition of bonds (cf. Mann, *loc. cit.*; Schwarzenbach, *loc. cit.*) is shown by the maximum value occurring with zinc. The stability increments decrease in the order Zn > Co > Ni $\gg$ Cu (the reverse of the usual order), there being a marked preference in the case of copper for the ligand trien which alone can form the desired coplanar chelate rings.

Increase in the size of a chelate ring from five to six or more members invariably decreases the stability (Irving, Williams, Ferrett, and Williams, *loc. cit.*), but there is no effect upon orders of stability (cf. Table 2). Comparison of data for ethylenediamine and propylenediamine shows that *C*-alkylation does not greatly alter chelating power. *N*-Alkylation, however, by increasing the interference volume of a ligand, tends to reduce stability; the effect is particularly noticeable in the increased difficulty of adding a second molecule of a bidentate ligand such as *NN'*-dimethylethylenediamine (cf. Table 2 and Irving *et al.*, *loc. cit.*). Similarly, the introduction of substituents $\alpha$ to one or both of the nitrogen atoms in 1 : 10-phenanthroline or its aza-derivatives (Irving and Williams, *Analyst*, 1952, **77**, 813) must oppose the close packing of ligand molecule around the central ion and so distort bond angles, increase metal–nitrogen distances, and reduce stability. The effect is immediately obvious in certain visual absorption spectra; thus, the addition of ferrous ions to phenanthroline or 2-methyl- or 2 : 9-dimethyl-phenanthroline gives deep red, pale yellow, and colourless solutions respectively, and measurements of stability constants (Table 2) show unequivocally the concomitant decreases in stability.

Steric effects which affect the ease of packing of ligands round a central ion will be specially sensitive to (*a*) structural modifications in the ligand, (*b*) the size of the central ion, and (*c*) the orbitals available, since these will impose, or tend to impose, a particular geometric arrangement of ligands. In exceptional cases such steric factors, assisted perhaps by orbital stabilisation through electronic rearrangements, may prevent the stability of metal ligands from following the normal order even within the first transition-metal series, and the possibility of designing ligands with the deliberate intention of exploiting these effects in analytical chemistry has already been envisaged (Irving and Williams, *loc. cit.*).

*Maximum Co-ordination Number.*—So far, no clear distinction has been drawn between stability sequences based upon over-all constants $\beta_N$ (where $N$ is the maximum co-ordination number) and those based upon, *e.g.*, values of $K_1$ or $\beta_2$ ($= K_1K_2$). In the first place $N$ itself is not constant for all the bivalent transition metals. Thus nickel and cobalt form hexammines whereas copper and zinc only form tetrammines, so that, whereas the Irving–Williams order holds for ammonia, for values of $K_1$, $K_2$, $K_3$, and $K_4$ through the whole series, and for $K_5$ and $K_6$ from manganese to nickel, there is a discontinuity at copper owing to the low value of $K_5$ and the negligible value of log $K_5$ for zinc. Similarly, the sequence holds for ethylenediamine for $K_1$ and $K_2$ but again fails at copper owing to the low value for log $K_3$. Similar effects may be seen with other polydentate ligands such as diethylenetriamine and probably ethylenediaminetetra-acetic acid. Owing to the great stability of copper complexes compared with those even of its neighbour nickel, values of log $\beta_N$ are normally greater for this element (even when $N = 4$) than for those of other transition elements, so the stability order is not often deranged and the significance of changes in maximum co-ordination have hitherto been to a large extent overlooked.

In conclusion, we would again point out that the "effective" co-ordination number (which Bjerrum, *op. cit.*, terms the "characteristic co-ordination number, $Z$") is dependent upon the ligand used. Thus with zinc it is clearly four in the case of ammonia, but six in the case of phenanthroline; with ethylenediamine the situation is intermediate, since the

first two ligands are added more readily than the third. In such cases the relative values of the ratio of successive stability constants, $K_n/K_{n+1}$, can provide a quantitative measure of steric hindrance, orbital changes, or changes in co-ordination number. Such data will be considered in a later paper.

*Entropy Effects.*—So far we have tacitly assumed that $-\Delta F$, the free-energy change which measures the stability of metal complexes, is dominated by the heat term, $-\Delta H$, of the corresponding process. But since $-2{\cdot}303\boldsymbol{R}T \log_{10} \beta = \Delta F = \Delta H - T\Delta S$, this assumption is equivalent to the statement that the entropy term $T\Delta S$ can be neglected in comparison with $\Delta H$. This simplifying assumption accords fairly well with the existing data on uncharged ligands, where the influence of the entropy term is insufficient to derange the " natural " order of stability of transition metal complexes. However, with reactions such as the following

$$M^{2+}(aq.) + nL^{-q}(aq.) \rightleftharpoons ML_n^{(2-nq)}(aq.) + mH_2O$$

there will be a net gain in entropy which may become of preponderating significance. But the most important single factor in the entropy change of such a reaction, *viz.*, the entropy of hydration of $M^{2+}$, increases as the radius of the transition ion decreases, *i.e.*, monotonically along the series manganese to copper (Latimer, *Chem. Reviews*, 1936, **18**, 355), so that the stabilising influence of the entropy change in the reaction will also follow the Irving–Williams order. This will no longer be true if other elements which break the monotonic sequence of ionic radius are included in our transition-metal stability order.

All the ligands discussed thus far have been the conjugate bases of weak acids, *i.e.*, their proton complexes have been more stable than the proton–water complex (hydroxonium ion); a similar stability has characterised their complexes with metals. But ligands such as $I^-$, $Br^-$, $Cl^-$, $H_2PO_4^-$, $PO_4^{3-}$, $SO_4^{2-}$, $ClO_4^-$, $BrO_3^-$, and $IO_3^-$, which are conjugate bases of strong acids, interact with protons less strongly than water does, and their interactions with metals are also feeble. Such ligands do not form strong complexes with transition metals because the heat of formation of the metal–ligand bond is comparable with, and often less than, the heat of formation of the metal–water bond. But in virtue of their negative charge there will be a partial or complete neutralisation of the positive charge on the cation on co-ordination, so that the entropy gain (see above) will, to a greater or less extent, offset the loss of interaction energy which occurs when water is replaced by such a ligand. The net free-energy change may be very small, and the resulting stability order might not necessarily follow the Irving–Williams order in the transition series. The closely similar stability constants for sulphate complexes should be noted in this connection (Table 2), and though the malonates clearly follow the natural order of stabilities, measurements for the zinc complex ($\Delta F = -5110$, $\Delta H = +3060$, $\Delta S = +27{\cdot}5$; James, *J.*, 1951, 153) show clearly that it is stabilised by the entropy term $\Delta S$. The same is true of the magnesium–malonate complex (Evans and Monk, *Trans. Faraday Soc.*, 1952, **48**, 934). For chloride ion complexes Bjerrum (*Chem. Reviews*, 1950, **46**, 381) quotes mean affinity constants of 1·0, 0·0, 0·6, and 1·5 for iron, cobalt, copper, and zinc, respectively, which suggest that the stability sequence has here been deranged and invalidated by the opposing influences of heat and entropy terms of comparable magnitude. However, the data may refer to complexes of the form of ion-pairs where—to make a formal distinction from the mode of complex formation discussed hitherto—the ligand molecule does not replace an equivalent number of water molecules in the hydration sheath immediately surrounding the cation. This aspect has been considered by one of us (Williams, *loc. cit.*) with special reference to the complexes of Group IIA metal ions.

In the following papers we shall show how steric effects or increases in the size of a chelate ring can reduce the stability of metal complexes without, however, deranging the stability order among the transition metals which we have shown to be a natural consequence of their ionisation potentials and ionic radii.

Inorganic Chemistry Laboratory, Oxford. [*Received, April 15th*, 1952.]

# 638. *Alkylperoxy-radicals. Part I. Reactions with 2 : 4 : 6-Trialkylphenols.*

By A. F. Bickel and E. C. Kooyman.

(*With an Appendix on the Spectroscopic Determination of the Structure of the Reaction Products.* By C. la Lau.)

Several types of alkylperoxy-radicals (RO·O·) were prepared both by cobalt-catalysed decompositions of the corresponding hydroperoxides (RO·OH) and by addition of alkyl radicals (R·) to oxygen. Their reactions with a number of 2 : 4 : 6-trialkylphenols (AH) have been investigated. The main products appeared to be peroxides (RO·OA) having the structure of alkylperoxy-2 : 4 : 6-trialkyl*cyclo*hexadienones. If a *p*-methyl group was present in the phenol, stilbenequinones were also formed. The results are discussed in relation to the inhibitory activity of phenols in autoxidation.

For most liquid-phase autoxidations of hydrocarbons the propagation sequence generally accepted is :

$$R\cdot + O_2 \longrightarrow RO\cdot O\cdot;\quad RO\cdot O\cdot + RH \longrightarrow RO\cdot OH + R\cdot$$

Termination may occur by interaction of the chain-carrying radicals (R· and RO·O·) or by reaction with an inhibitor (Bolland, *Quart. Reviews*, 1949, **3**, 1). The amounts of inhibitor required to suppress oxygen absorption are generally very small—often as little as 0·01%—probably as a result of the large overall kinetic chain lengths. In consequence, the amounts of products formed from the inhibitor are too small for a detailed study, which seriously handicaps investigations into the mode of action of antioxidants.

Abundant evidence is available (Bolland, *loc. cit.*) as regards the predominating part played by alkylperoxy-radicals (RO·O·) in autoxidation. Since the concentration of alkyl radicals (R·) is generally low as a result of their rapid reaction with oxygen to form alkylperoxy-radicals, it seems plausible to assume the inhibitor to operate mainly by reactions with RO·O·. In order to investigate the latter reactions by isolation of products, methods are required for the preparation of alkylperoxy-radicals on a sufficient scale while avoiding the simultaneous oxidation of an excess of other products. Recent literature has dealt to some extent with methods of this kind. Cosgrove and Waters (*J.*, 1951, 388) investigated the oxidation of phenols with benzoyl peroxide and related their results to the mechanism of inhibition and retardation by alkylphenols. Since the benzoyloxy-radical is not quite comparable to the alkylperoxy-radicals involved in autoxidation of hydrocarbons their conclusions need further support. While the present investigation was in progress, Campbell and Coppinger (*J. Amer. Chem. Soc.*, 1952, **74**, 1469) reported the interaction of *tert.*-butyl hydroperoxide and alkylphenols under the influence of cobalt naphthenate. However, only one product was isolated and its structure was not definitely proved.

The present paper deals with the interactions of a number of 2 : 4 : 6-trialkylphenols with various alkylperoxy-radicals.

*Production of Alkylperoxy-radicals and Their Reaction with 2 : 4 : 6-Trialkylphenols.*—The generation of alkylperoxy-radicals and their reaction with phenolic inhibitors was achieved : (*a*) by decomposition of alkyl hydroperoxides dissolved in benzene by cobalt naphthenate at room temperature in the presence of a 2 : 4 : 6-trialkylphenol, and (*b*) by thermal decomposition in benzene solution of compounds producing alkyl radicals in the presence of oxygen and a 2 : 4 : 6-trialkylphenol.

Reactions of type (*a*) were carried out with *tert.*-butyl, 1-tetralyl, αα-dimethylbenzyl, 1 : 1-diphenylethyl, and triphenylmethyl hydroperoxide. The phenols investigated were 2 : 4 : 6-trimethyl-, 2-*tert.*-butyl-4 : 6-dimethyl-, 4-*tert.*-butyl-2 : 6-dimethyl-, 2 : 4-di-*tert.*-butyl-6-methyl-, 2 : 6-di-*tert.*-butyl-4-methyl-, and 2 : 4 : 6-tri-*tert.*-butyl-phenol.

Two mols. of the hydroperoxide (RO·OH) and one mol. of the phenol (AH) were dissolved in benzene, and small quantities of cobalt naphthenate (Co content 15%) (2—4 g. in all) were added until the reaction was complete (temperature between 20° and 30°). The

residue obtained on evaporation *in vacuo* was crystallized or distilled in a high vacuum. In most cases it was possible to obtain pure compounds RO·OA, the reactions involved being:

$$RO{\cdot}OH + Co^{+++} \longrightarrow RO{\cdot}O{\cdot} + H^{+} + Co^{++} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RO{\cdot}OH + Co^{++} \longrightarrow RO{\cdot} + OH^{-} + Co^{+++} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$RO{\cdot}O{\cdot} + AH \longrightarrow (RO{\cdot}OAH){\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$(RO{\cdot}OAH){\cdot} + RO{\cdot} \longrightarrow RO{\cdot}OA + ROH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Overall: $2RO{\cdot}OH + AH \longrightarrow RO{\cdot}OA + ROH + H_2O \quad . \quad . \quad . \quad . \quad . \quad (5)$

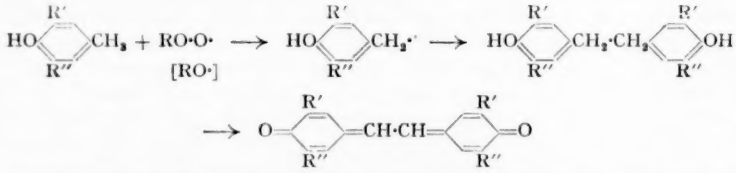
Instead of reactions 3 and 4, hydrogen abstraction from the inhibitor may be the first step, the resulting A· radical then combining with RO·O· to give the same products:

$$RO{\cdot} + AH \longrightarrow ROH + A{\cdot}$$
$$A{\cdot} + RO{\cdot}O{\cdot} \longrightarrow RO{\cdot}OA$$

The experimental fact that only catalytic quantities of cobalt naphthenate are necessary for the reaction is expressed by the overall equation (5). Apparently, alkyloxy- and alkylperoxy-radicals are produced in equivalent quantities, the former serving as hydrogen acceptors and yielding an equimolar amount of alcohol. The quantity of alcohol was checked in an experiment with *tert.*-butyl hydroperoxide and an excess of 2 : 6-di-*tert.*-butyl-4-methylphenol; it was proved to be exactly half the amount of the hydroperoxide used.

More than one peroxide may be formed from a 2 : 4 : 6-trialkylphenol; 2 : 4-di-*tert.*-butyl-6-methylphenol and *tert.*-butyl hydroperoxide give a yellow compound of m. p. 70° and a colourless peroxide of m. p. 34°, both having the formula $C_{19}H_{32}O_3$, in yields of 32% and 26% respectively (Table).

Apart from peroxides RO·OA, stilbenequinones are sometimes formed. They must result from an attack of the alkylperoxy- or alkoxy-radical on a *p*-methyl group, followed by dimerization and subsequent dehydrogenation, *e.g.*:



Compounds of this type were isolated when 2 : 4 : 6-trimethyl- and 2-*tert.*-butyl-4 : 6-dimethyl-phenol were treated with hydroperoxides. 2 : 6-Di-*tert.*-butyl-4-methylphenol, though also possessing a *p*-methyl group, did *not* yield a stilbenequinone with most hydroperoxides, but it did so with triphenylmethyl hydroperoxide.

The thermal decomposition (*b*) of compounds producing alkyl radicals, and reaction of the latter with oxygen and inhibitor, were carried out in the following manner: Benzene solutions of 2 : 2′-azo*iso*butyronitrile or 2 : 2 : 3 : 3-tetraphenylbutane and an equimolar quantity of 2 : 4 : 6-trialkylphenol were heated at 60—80° in the presence of a large excess of oxygen until the reaction was complete.* The residue obtained on evaporation was crystallized to yield pure products. When 2 : 6-di-*tert.*-butyl-4-methylphenol was the inhibitor, peroxides could be obtained in the pure state. The reactions are:

$$R{\cdot}N{:}N{\cdot}R \longrightarrow 2R{\cdot} + N_2 \quad [R = Me_2(CN)C{\cdot}]$$
$$R{\cdot}R \rightleftarrows 2R{\cdot} \quad [R = Ph_2MeC{\cdot}]$$
$$2R{\cdot} + 2O_2 \longrightarrow 2RO{\cdot}O{\cdot}$$
$$RO{\cdot}O{\cdot} + AH \longrightarrow (RO{\cdot}OAH){\cdot}$$
$$(RO{\cdot}OAH){\cdot} + RO{\cdot}O{\cdot} \longrightarrow RO{\cdot}OA + RO{\cdot}OH$$

Overall: $2R{\cdot} + 2O_2 + AH \longrightarrow RO{\cdot}OA + RO{\cdot}OH$

* The time required to obtain a nearly quantitative production of radicals was calculated from the half-life values of azo-compound and hydrocarbon.

In the reaction of 2 : 6-di-*tert.*-butyl-4-methylphenol with 2 : 2 : 3 : 3-tetraphenylbutane and oxygen both the peroxide and the hydroperoxide could be isolated in yields of over 80%. The same phenol, 2 : 2′-azo*iso*butyronitrile, and oxygen gave a peroxide containing the 1-cyano-1-methylethylperoxy-group, in 54% yield. Peroxides could not be obtained by treating the azo-nitrile with oxygen and other 2 : 4 : 6-trialkylphenols; 2-*tert.*-butyl-4 : 6-dimethylphenol yielded a stilbenequinone which was identical with that obtained in the reaction with *tert.*-butyl hydroperoxide. 2 : 4 : 6-Tri-*tert.*-butylphenol gave 2 : 6-di-*tert.*-butylbenzoquinone among other products.

The above reaction schemes are strongly supported by the finding that the same peroxide $Ph_2MeC{\cdot}O{\cdot}OA$ was obtained from 2 : 6-di-*tert.*-butyl-4-methylphenol and (i) the hydroperoxide $Ph_2MeC{\cdot}O{\cdot}OH$ or (ii) $Ph_2MeC{\cdot} + O_2$.

The yields of the products obtained by methods (*a*) and (*b*) are given in the Table.

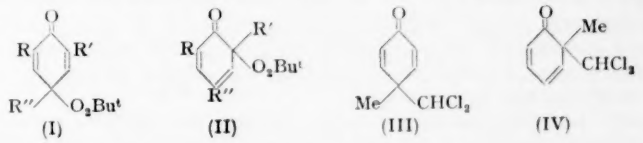
*Yields* (%) *of peroxides from alkyl hydroperoxides and* 2 : 4 : 6-*trialkylphenols.*

| | 2 : 4 : 6-Trialkylphenols | | | | | |
|---|---|---|---|---|---|---|
| Hydroperoxides | 2 : 4 : 6-$Me_3$ | 2-$Bu^t$-4 : 6-$Me_2$ | 4-$Bu^t$-2 : 6-$Me_2$ | 2 : 4-$Bu^t_2$-6-Me | 2 : 6-$Bu^t_2$-4-Me | 2 : 4 : 6-$Bu^t_3$ |
| $Bu^tO{\cdot}OH$ ... | 7 (3·9 [e]) (52 [a]) | 25 (3·5 [e]) (20 [a]) | 46 (1·8 [e]) 13 [d] (3·5 [e]) | 26 (1·85 [e]) 32 [d] (2·7 [e]) | 100 (3·85 [e]) — | 90 (1·9 [e]) — |
| 1-Tetralyl ..... | — | — | 11 | 33 | 55 | — |
| $PhMe_2C{\cdot}O{\cdot}OH$... | — | — | — | — | 40 | 48 |
| $Ph_2MeC{\cdot}O{\cdot}OH$... | — | — | — | — | 53 | — |
| $Ph_3C{\cdot}O{\cdot}OH$ ..... | — | — | — | — | 45 [a] | — |
| $(NC{\cdot}CMe_2{\cdot}CN)_2$ + $O_2$ ..... | — | 13 [a] | — | — | 54 | 37 [b] |
| $(CPh_2Me)_2 + O_2$ | — | — | — | — | 85 | — |

[a] Stilbenequinone. [b] 2 : 6-Di-*tert.*-butylbenzoquinone. [e] Equivs. of hydriodic acid consumed by the peroxides. [d] 2-*tert.*-Butylperoxy-2-methyl-ketones.

*Structure of the Peroxidic Products.*—The peroxides RO·OA are coloured liquids or colourless crystalline solids, stable at room temperature but often very sensitive to light, which causes a marked discoloration.

The structure of the products containing a *tert.*-butylperoxy-group has been investigated. The peroxy-group is demonstrated by explosive decomposition at 120—150°. The ultraviolet spectra reveal two types of conjugated double-bond systems, and have been shown to be due to structures (I) and (II) by comparison with the spectra of appropriate model




(I) (II) (III) (IV)

compounds (III) and (IV). The products are all of type (I), except that those covered by footnote *d* in the Table are of type (II). The structure (II) of a yellow peroxide from 2 : 4-di-*tert.*-butyl-6-methylphenol was confirmed by the infra-red spectra in the 6-$\mu$ region.

The absence of hydroxyl groups was demonstrated by infra-red analysis; this, again, is in agreement with the assigned structures which exclude enolization.

Hydriodic acid reduction revealed interesting differences. Thus, some of the peroxides consume two and others four equivalents of the acid. It appears that those products having a *tert.*-butyl and a *tert.*-butylperoxy-group on the same carbon atom use only two equivalents, whilst the combination of methyl and *tert.*-butylperoxy-groups is connected with a consumption of 3—4 mols. (see Table).

Only some of the reduction products could be isolated. The ketone (I; R = R′ = Me, R″ = $Bu^t$) gave 2 : 6-dimethylquinol, and (I; R = R′ = $Bu^t$, R″ = Me) and 2 : 6-di-*tert.*-butyl-4(?)-(1-cyano-1-methylethylperoxy)-4-methyl*cyclo*hexadienone gave 2-*tert.*-butyl-4-methylphenol, all in quantitative yield. A small amount of *tert.*-butylquinol was obtained from (I; R = R′ = R″ = $Bu^t$). The other peroxy-compounds did not yield pure products.

Reduction of (I; R = R′ = Me, R″ = Bu$^t$) and of (I; R = R′ = Bu$^t$, R″ = Me) with octane-1-thiol at 160° regenerated the original phenol.

*Differences Between the Various Phenols in Their Reactions with Alkylperoxy-radicals.*—Considerable evidence is available with regard to the marked influence of structure on antioxidant efficiencies of alkylphenols (*e.g.*, Wasson and Smith, *Ind. Eng. Chem.*, 1953, **45**, 197; Rosenwald, Hoatson, and Chenicek, *ibid.*, 1950, **42**, 162). However, in inhibited autoxidations of hydrocarbons the antioxidant and the hydrocarbon compete for the alkylperoxy-radicals, whereas the present results are limited to the interaction of the latter radicals and the antioxidants, giving no information on reaction rates.

On the other hand, some interesting differences may be deduced from the Table. Thus, the data presented in the first row (reactions with *tert.*-butyl hydroperoxide and cobalt naphthenate) indicate a decrease in yield of stilbenequinones and an increase in the yield of Bu$^t$O·OA to occur in the series 2 : 4 : 6-Me$_3$, 2-Bu$^t$-4 : 6-Me$_2$, 2 : 6-Bu$^t_2$-4-Me.

A stilbenequinone is produced in the reaction of triphenylmethyl hydroperoxide and 2 : 6-di-*tert.*-butyl-4-methylphenol, whereas all other hydroperoxides yield peroxides RO·OA with this phenol.

## Experimental [With W. Roest and P. Piet]

*Starting Materials.*—tert.-*Butyl hydroperoxide.* The crude material, containing about 40% of hydroperoxide, was distilled in a 3-m. Vigreux column, to yield a fraction, b. p. 35—36°/17 mm. (96% of hydroperoxide by iodometric titration).

1-*Tetralyl hydroperoxide.* Tetralin, mixed with 0·02% of cobalt naphthenate, was oxidized with air until at least 20% of the hydroperoxide had been formed. Excess of tetralin was removed in a high vacuum and the residue recrystallized from toluene (m. p. 54—55°; purity >95%).

αα-*Dimethylbenzyl hydroperoxide.* The crude material (75% of hydroperoxide) was purified *via* the sodium salt. Distillation in a high vacuum gave a fraction, b. p. 68—69°/0·08 mm. (97% pure).

1 : 1-*Diphenylethyl hydroperoxide.* This was obtained as a by-product in the reaction of 2 : 6-di-*tert.*-butyl-4-methylphenol with 2 : 2 : 3 : 3-tetraphenylbutane and oxygen. Recrystallization from light petroleum gave a colourless product of m. p. 84°.

Triphenylmethyl hydroperoxide, prepared according to Wieland and Maier (*Ber.*, 1931, **64**, 1205), had m. p. 82°.

2 : 2′-Azo*iso*butyronitrile was synthesized as directed by Bickel and Waters (*Rec. Trav. chim.*, 1950, **69**, 1490).

2 : 2 : 3 : 3-*Tetraphenylbutane.* The directions of Ziegler *et al.* (*Annalen*, 1924, **437**, 227; 1942, **551**, 150) were followed. Slight modifications increased the yield to 80%.

2 : 4 : 6-Trimethylphenol, obtained according to the method of Barclay, Burawoy, and Thomson (*J.*, 1944, 400), had m. p. 72—73°.

6-*tert.*-Butyl-2 : 4-dimethylphenol was purified by extraction with 10% potassium hydroxide solution, distillation *in vacuo* (b. p. 122—128°/14 mm.), and several crystallizations from light petroleum (b. p. 60—80°). The m. p. of the colourless material was 22·5°.

4-*tert.*-Butyl-2 : 6-dimethyl-, 2 : 4-di-*tert.*-butyl-6-methyl,- and 2 : 4 : 6-tri-*tert.*-butyl-phenol were prepared by alkylation of 2 : 6-dimethylphenol, *o*-cresol, and phenol respectively with *tert.*-butanol and sulphuric acid at 70°. M. p.s of the recrystallized products were 82·5°, 52·5°, and 129—130° respectively.

2 : 6-Di-*tert.*-butyl-4-methylphenol of technical quality, when distilled with steam and recrystallized from methanol, had m. p. 71·0°.

### *Reactions of hydroperoxides with 2 : 4 : 6-trialkylphenols.*

*General Procedure.*—The phenol (0·1 mole) and the hydroperoxide (0·2 mole) were dissolved in 100 ml. of dry, thiophen-free benzene in a brown bottle. Addition of cobalt naphthenate in 200-mg. portions was continued until the temperature, which was held between 20° and 30°, remained constant. At this stage the residual hydroperoxide content was measured by iodometric titration of a sample; it was usually lower than 0·01 mole. The mixture was filtered and the solvent and volatile products were evaporated *in vacuo* (40°/0·25 mm.). The residue was recrystallized or distilled in a high vacuum.

*Reactions of* tert.-*Butyl Hydroperoxide.*—(a) *With 2 : 4 : 6-trimethylphenol.* The dark-red

insoluble crystals of 3 : 5 : 3′ : 5′-tetramethylstilbene-4 : 4′-quinone, filtered and washed with benzene, had m. p. 220° (decomp.) (Found : C, 81·0; H, 6·9. Calc. for $C_{18}H_{18}O_2$ : C, 81·2; H, 6·8%). Distillation of the mother-liquor yielded an oil boiling at 60—80°/1·2 mm. It crystallized from methanol at −70°, producing 4-tert.-*butylperoxy*-2 : 4 : 6-*trimethyl*cyclo*hexa*-2 : 5-*dienone*, m. p. 74° (Found : C, 69·4; H, 9·3. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%).

(b) *With* 2-tert.-*butyl*-4 : 6-*dimethylphenol*. The red, liquid residue was treated with methanol, and the brick-red crystals of 3 : 3′-*dimethyl*-5 : 5′-*di*-tert.-*butylstilbene*-4 : 4′-*quinone* were filtered off and washed with the same solvent; they had m. p. 230° (decomp.) (Found : C, 82·7; H, 8·7. $C_{24}H_{30}O_2$ requires C, 82·3; H, 8·6%). The mother-liquor was distilled in a high vacuum, yielding a yellow-orange fraction, b. p. 62—63°/0·2 mm. The analysis indicates a tert.-*butyl*-tert.-*butylperoxy*-*dimethyl*cyclo*hexadienone* (Found : C, 72·3; H, 9·5. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%), but the ultra-violet absorption spectrum indicates unknown impurities in addition to the 4-*tert.*-butylperoxy-compound, whereas the 2-*tert.*-butylperoxy-structure is not likely to be present.

(c) *With* 4-tert.-*butyl*-2 : 6-*dimethylphenol*. The partly crystalline residue was recrystallized from ethanol at −70°, yielding 4-tert.-*butyl*-4-tert.-*butylperoxy*-2 : 6-*dimethyl*cyclo*hexa*-2 : 5-*dienone*, m. p. 78° (Found : C, 71·7; H, 9·8%). A second crop was obtained by distilling the mother-liquor in a high vacuum. The partly crystalline distillate, b. p. 94°/1 mm., was again recrystallized from ethanol; the crystals also melted at 78°. Distillation of the final mother-liquor gave an orange liquid, b. p. 83°/0·5 mm. Its analysis is correct for a tert.-*butyl*-tert.-*butylperoxy*-*dimethyl*cyclo*hexadienone* (Found : C, 71·5; H, 9·7%). According to the ultra-violet spectrum it may have the 2-*tert.*-butylperoxy-structure, whilst the 4-*tert.*-butylperoxy-derivative is absent.

(d) *With* 2 : 4-*di*-tert.-*butyl*-6-*methylphenol*. The partly crystalline residue was treated with methanol at −70° and filtered, yielding yellow 2 : 4-*di*-tert.-*butyl*-6-tert.-*butylperoxy*-6-*methyl*cyclo*hexa*-2 : 4-*dienone*, m. p. 70° (Found : C, 74·0; H, 10·5. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·5%). The mother-liquor was distilled in a high vacuum, the fraction of b. p. 90°/0·5 mm. yielding colourless 2 : 4-*di*-tert.-*butyl*-4-tert.-*butylperoxy*-6-*methyl*cyclo*hexa*-2 : 5-*dienone*, m. p. 34°, after crystallization from ethanol at −70° (Found : C, 74·1; H, 10·4%).

(e) *With* 2 : 6-*di*-tert.-*butyl*-4-*methylphenol*. Recrystallization of the residue from ethanol gave 2 : 6-di-*tert.*-butyl-4-*tert.*-butylperoxy-4-methyl*cyclo*hexa-2 : 5-dienone, m. p. 87° (Found : C, 74·4; H, 10·6%). Campbell and Coppinger (*J. Amer. Chem. Soc.*, 1952, **74**, 1469) have recorded m. p. 74°. Hydrogenation over Adams catalyst in glacial acetic acid, removal of the solvent *in vacuo*, and crystallization from ethanol produced a *dihydro*-derivative, m. p. 78—79° (Found : C, 73·5; H, 11·2. $C_{19}H_{34}O_3$ requires C, 73·5; H, 11·0%). This product still contains the peroxy-grouping.

The amount of *tert.*-butanol formed was determined in a separate experiment with 0·050 mole each of hydroperoxide and phenol. Benzene and the volatile products were distilled and dried ($Na_2SO_4$). *tert.*-Butanol was determined spectroscopically (Found : 0·0252 mole).

(f) *With* 2 : 4 : 6-*tri*-tert.-*butylphenol*. The liquid, green-yellow residue was crystallized from methanol at −70°, yielding green-yellow 2 : 4 : 6-*tri*-tert.-*butyl*-4-tert.-*butylperoxy*cyclo*hexa*-2 : 5-*dienone*, m. p. 5° (Found : C, 75·3; H, 11·0. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%). According to the ultra-violet absorption spectrum this preparation may contain some of the 2-*tert.*-butylperoxy-derivative. Distillation of the mixture in a high vacuum gave a brown-green liquid, b. p. 85°/0·15 mm., which gave correct analyses but could not be crystallized. An attempt to hydrogenate this peroxide over Adams catalyst in acetic acid was unsuccessful.

*Reactions of* 1-*Tetralyl Hydroperoxide*.—(a) *With* 4-tert.-*butyl*-2 : 6-*dimethylphenol*. Treatment of the residue with ethanol produced yellow 4-tert.-*butyl*-2 : 6-*dimethyl*-4(?)-1′-*tetralylperoxy*cyclo*hexadienone*, m. p. 104° (Found : C, 77·8; H, 8·4. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%).

(b) *With* 2 : 4-*di*-tert.-*butyl*-6-*methylphenol*. The residual syrup was diluted with an equal volume of ethanol; the resulting yellow crystals of 2 : 4-*di*-tert.-*butyl*-6-*methyl*-4(?)-1′-*tetralylperoxy*cyclo*hexadienone* had m. p. 91° after recrystallization from methanol (Found : C, 78·7; H, 9·0. $C_{25}H_{34}O_3$ requires C, 78·5; H, 9·0%). The mother-liquor yielded a product, m. p. 95°, which proved to be identical with the peroxide of m. p. 91° (mixed m. p. 93°). The m. p. of the first product could also be raised to 95° by repeated recrystallizations.

(c) *With* 2 : 6-*di*-tert.-*butyl*-4-*methylphenol*. The residue was recrystallized from methanol, yielding 2 : 6-*di*-tert.-*butyl*-4-*methyl*-4(?)-1′-*tetralylperoxy*cyclo*hexadienone*, m. p. 104° (Found : C, 78·7; H, 8·8%).

*Reactions of* αα-*Dimethylbenzyl Hydroperoxide*.—(a) *With* 2 : 6-*di*-tert.-*butyl*-4-*methylphenol*.

The residue, in light petroleum, was extracted with 2N-hydrochloric acid in order to remove cobalt salts. Evaporation of the solvent produced a syrup which was crystallized from methanol at −70°. Recrystallization from ethanol yielded colourless 2 : 6-*di*-tert.-*butyl*-αα-*dimethylbenzylperoxy*-4-*methyl*cyclo*hexadienone*, m. p. 42·5° (Found: C, 77·8; H, 9·3. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

(b) *With* 2 : 4 : 6-*tri*-tert.-*butylphenol*. Cobalt was removed as previously described. Crystallization from ethanol gave yellow 2 : 4 : 6-*tri*-tert.-*butyl*-4(?)-αα-*dimethylbenzylperoxy*cyclo*hexadienone*, m. p. 35° (Found: C, 78·7; H, 9·8. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·8%).

*Reaction of* 1 : 1-*Diphenylethyl Hydroperoxide with* 2 : 6-*Di*-tert.-*butyl*-4-*methylphenol*.—Cobalt was extracted with hydrochloric acid. Crystallization of the residue from ethanol at −15° gave colourless 2 : 6-*di*-tert.-*butyl*-4(?)-(1 : 1-*diphenylethylperoxy*)-4-*methyl*cyclo*hexadienone*, m. p. 67° (Found: C, 80·4; H, 8·5. $C_{29}H_{36}O_3$ requires C, 80·5; H, 8·4%). The mother-liquor was evaporated and the residue treated with light petroleum. The light brown crystals obtained had m. p. 80·5° (with 1 : 1-diphenylethanol, mixed m. p. 80·5—81°).

*Reaction of Triphenylmethyl Hydroperoxide with* 2 : 6-*Di*-tert.-*butyl*-4-*methylphenol*.—The red crystalline residue of 3 : 5 : 3′ : 5′-tetra-*tert.*-butylstilbene-4 : 4′-quinone was washed with ethanol and recrystallized from glacial acetic acid; it had m. p. 303° (decomp.) (Found: C, 82·8; H, 9·7. Calc. for $C_{30}H_{42}O_2$: C, 82·9; H, 9·7%).

*Reactions of* 2 : 2′-*azo*isobutyronitrile *and* 2 : 2 : 3 : 3-*tetraphenylbutane with oxygen and* 2 : 4 : 6-*trialkylphenols.*

*General Procedure*.—The phenol (0·1 mole) and the nitrile or butane (0·1 mole) were dissolved in dry, thiophen-free benzene (150 ml.) and a rapid stream of dry oxygen was bubbled through the solution by means of a sintered-glass plate for 6 hr. at 80° or 60°. The reaction mixture was evaporated in *vacuo* (40°/0·25 mm.).

*Reactions of the Nitrile*.—(a) *With* 2-tert.-*butyl*-4 : 6-*dimethylphenol and oxygen*. Methanol was added to the residue, and the red crystals of 5 : 5′-di-*tert.*-butyl-3 : 3′-dimethylstilbene-4 : 4′-quinone were filtered off. They had m. p. 230° (decomp.) after recrystallization from ethyl methyl ketone.

(b) *With* 2 : 6-*di*-tert.-*butyl*-4-*methylphenol and oxygen*. The crude material was recrystallized from methanol, yielding colourless 2 : 6-*di*-tert.-*butyl*-4(?)-(1-*cyano*-1-*methylethylperoxy*)-4-*methyl*cyclo*hexadienone*, m. p. 92·5° (Found: C, 71·9; H, 9·6; N, 4·4. $C_{19}H_{29}O_3N$ requires C, 71·5; H, 9·2; N, 4·4%).

(c) *With* 2 : 4 : 6-*tri*-tert.-*butylphenol and oxygen*. Distillation of the residue with steam produced orange-yellow crystals, m. p. 68° after recrystallization from methanol (Found: C, 76·1; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%). Reduction with zinc in boiling 90% acetic acid yielded a *quinol*, m. p. 103° (from light petroleum) (Found: C, 75·7; H, 9·9. $C_{14}H_{22}O_2$ requires C, 75·6; H, 9·9%). The oxidation product of m. p. 68° should therefore be 2 : 6-*di*-tert.-*butylbenzoquinone*, since the derived quinol is not identical with 2 : 5-di-*tert.*-butylquinol, m. p. 216°.

*Reaction of* 2 : 2 : 3 : 3-*Tetraphenylbutane with* 2 : 6-*Di*-tert.-*butyl*-4-*methylphenol and Oxygen*.—Light petroleum was added to the residue, yielding crystals of 1 : 1-diphenylethyl hydroperoxide (93%). Recrystallization from the same solvent raised the m. p. to 84°. The filtrate was evaporated *in vacuo* and the residue treated with ethanol. The colourless crystals of 2 : 6-di-*tert.*-butyl-4(?)-(1 : 1-diphenylethylperoxy)-4-methyl*cyclo*hexadienone had m. p. 67° after recrystallization and were identical with those obtained by reaction of the phenol with 1 : 1-diphenylethyl hydroperoxide.

*Reduction of peroxidic products.*

*General Procedure with Hydriodic Acid*.—The peroxide (6·0 g.) was dissolved in acetic acid (200 ml.), mixed with freshly distilled 57% hydriodic acid (60 ml.), kept at 65° for 45 min., and then poured into water. Iodine was removed with concentrated sodium thiosulphate solution, and the excess of hydriodic acid neutralized with sodium hydroxide. Reduction products were extracted with ether.

*Reduction of* (I; R = R′ = Me, R″ = Bu$^t$).—The crude product, recrystallized several times from toluene, had m. p. 148—149° (Found: C, 69·5; H, 7·3. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·3%), alone or mixed with 2 : 6-dimethylquinol.

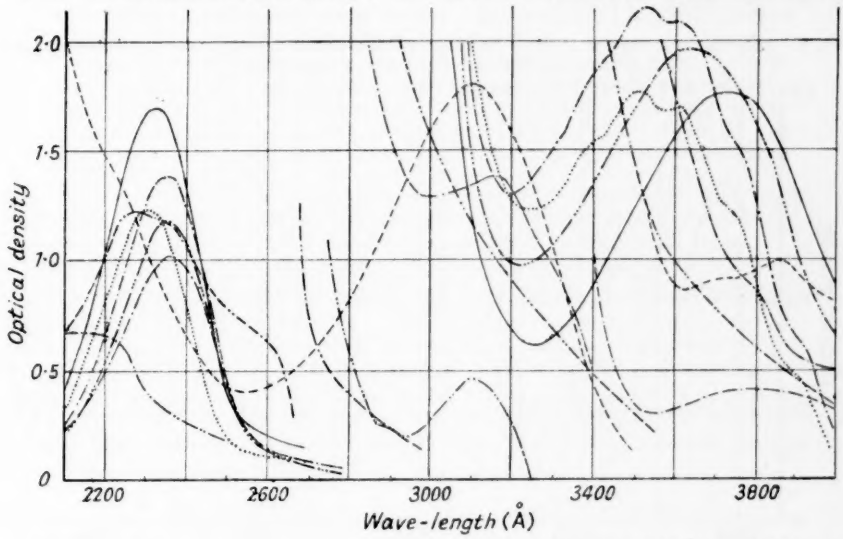
*Reduction of* (I; R = R′ = Bu$^t$, R″ = Me).—The residual oil, crystallized from light petroleum, had m. p. 52° (Found: C, 80·2; H, 10·0. Calc. for $C_{11}H_{16}O$: C, 80·4; H, 9·8%). It was 2-*tert.*-butyl-4-methylphenol (mixed m. p.).

*Reduction of* (I; R = R′ = R″ = Bu$^t$).—The crude product, *tert.*-butylquinol, recrystallized three times from toluene, had m. p. and mixed m. p. 127—128° (Found : C, 72·4; H, 8·4. Calc. for $C_{10}H_{14}O_2$ : C, 72·3; H, 8·5%).

*Reduction of* 2 : 6-*Di*-tert.-*butyl*-4(?)-(1-*cyano*-1-*methylethylperoxy*)-4-*methyl*cyclo*hexadienone.*—2-*tert.*-Butyl-4-methylphenol was isolated as described above.

*Reductions with Octane*-1-*thiol.*—Octane-1-thiol (150 g.) was kept at 160—170° and 0·05 mole of the peroxide was added in small portions. The excess of thiol was removed at 20 mm. and the residue was treated with a solution of iodine in benzene to oxidize residual thiol to disulphide. The reduction product was then distilled in a high vacuum.

FIG. 1. *Ultra-violet absorption spectra of* tert.-*butylperoxy*-2 : 4 : 6-*trialkyl*cyclo*hexadienones.*




| Compounds (I) R | R′ | R″ | Curve | Concns. (g./l.) (4000 → 2100 Å); cell thickness (cm.) in parentheses | | | |
|---|---|---|---|---|---|---|---|
| Me | Me | Me | ····· | 4·18 (5) | 0·0209 (1) | | |
| Me | Bu$^t$ | Me | – – · · · · · | 1·40 (5) | 1·40 (1) | 0·140 (1) | 0·280 (1) |
| Me | Me | Bu$^t$ | — · — · — · — | 5·28 (5) | 0·0264 (1) | | |
| Bu$^t$ | Me | Bu$^t$ | — · · · — · · · — | 5·74 (5) | 0·0287 (1) | | |
| Bu$^t$ | Bu$^t$ | Me | ——— | 4·80 (5) | 0·0480 (1) | | |
| Bu$^t$ | Bu$^t$ | Bu$^t$ | – – · – – · | 3·30 (1) | 1·65 (1) | 0·0330 (1) | |
| Compounds (II) R | R′ | R″ | | | | | |
| Me | Me | Bu$^t$ | · · — · · — · · | 2·40 (5) | 2·40 (1) | 0·0240 (1) | |
| Bu$^t$ | Me | Bu$^t$ | — — — ——— | 0·750 (2·5) | 0·150 (1) | | |

The crude product from (I; R = R′ = Me, R″ = Bu$^t$) had a boiling range of 70—130°/0·2 mm. and solidified partly. Filtration and washing with light petroleum gave a 52% yield of 4-*tert.*-butyl-2 : 6-dimethylphenol.

The crude material from (I; R = R′ = Bu$^t$, R″ = Me) boiled at 80—90°/0·3 mm. Seeding with 2 : 6-di-*tert.*-butyl-4-methylphenol yielded crystals (60%), m. p. 70°.

## Spectroscopy of *tert.*-butylperoxy-2 : 4 : 6-trialkyl*cyclo*hexadienones.

By C. la Lau.

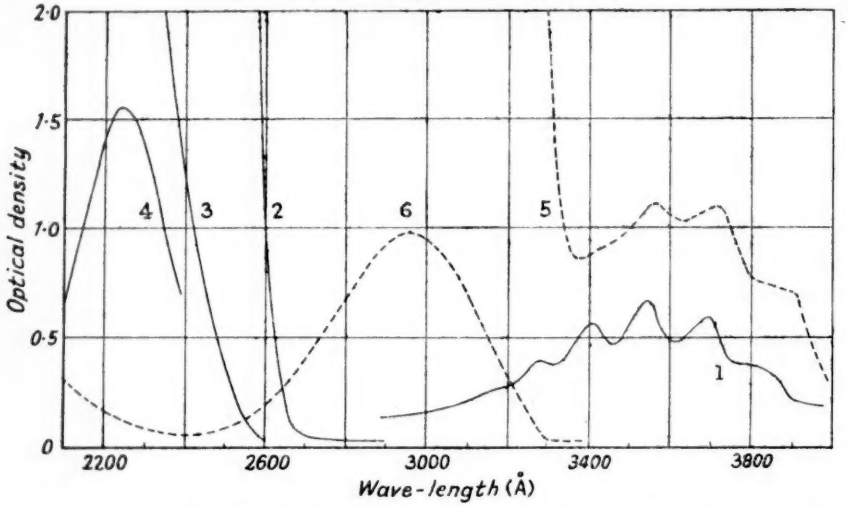
The ultra-violet absorption spectra of the peroxidic products in *iso*octane were recorded from 2100 to 4000 Å on a Cary-UV-recording spectrometer. They are shown in Fig. 1. The ultra-violet spectra of the reference compounds (III) and (IV) are in Fig. 2. Infrared absorption spectra from 5·7 to 6·2 μ were investigated with a Beckman-IR-2

spectrometer with a lithium fluoride prism and carbon tetrachloride as solvent. Concentrations of 10% and a cell length of 0·096 mm. were used throughout.

Although additional work was carried out on the presence of hydroxyl groups and peroxy-linkages the spectroscopic data will not be presented, since they scarcely contributed to elucidation of structures.

Comparison of the ultra-violet spectra of the peroxides with those of (III) and (IV) shows the presence of the two types (I) and (II). Infra-red analysis shows the absence of hydroxyl groups in all compounds—enolization could occur only with a *meta*-substituted *tert.*-butylperoxide. Moreover, enolization would lead to an alkyl-phenol with a strong band around 2800 Å characteristic of the benzene nucleus. The ultra-violet spectra clearly show that such bands are absent.

FIG. 2. *Ultra-violet absorption spectra of* 4-*dichloromethyl*-4-*methyl*cyclo*hexa*-2 : 5-*dienone* (III) *and* 2-*dichloromethyl*-2-*methyl*cyclo*hexa*-3 : 5-*dienone* (IV).




| | Concn. (g./l.) | Cell thickness (cm.) | | Concn. (g./l.) | Cell thickness (cm.) |
|---|---|---|---|---|---|
| (III), 1 | 1·934 | 5 | (IV), 5 | 1·922 | 1 |
| 2 | 1·934 | 1 | 6 | 0·0384 | 1 |
| 3 | 0·0386 | 1 | | | |
| 4 | 0·0193 | 1 | | | |

The introduction of one or more *tert.*-butyl groups *ortho* to the carbonyl group removes the fine structure exhibited in the weak band around 3700 Å, in accordance with previous experience. If the fine structure is neglected, the main absorption regions are only slightly affected by the nature of the substituents.

The spectra prove the structures allotted in the preceding sections.

Although less promising than the ultra-violet region the so-called infra-red double-bond region was included, since all the samples have complicated double-bond systems. However, it did not provide a general means of discriminating between (I) and (II); they depended on the conjugated systems as well as on the nature of the substituents. The only compound known from the ultra-violet spectrum to be of type (II) did *not* exhibit the intense band at 6·07 $\pm$ 0·004 $\mu$ present in all the compounds of type (I). This result, though of no great importance, is in agreement with the conclusions drawn from the ultra-violet data.

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KONINKLIJKE/SHELL-LABORATORIUM, AMSTERDAM. [*Received, May 28th,* 1953.]

## 639. *Reactions of Fluorocarbon Radicals. Part XI.* Synthesis and Some Reactions of Trifluoromethanethiol and Trifluoromethanesulphenyl Chloride.*

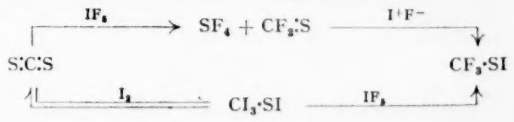
By R. N. Haszeldine and J. M. Kidd.

Reaction of carbon disulphide with iodine pentafluoride gives mainly bistrifluoromethyl disulphide and sulphur tetrafluoride. Bistrifluoromethyl trisulphide is a by-product and together with bistrifluoromethyl tetrasulphide is a product from the reaction of trifluoroiodomethane with sulphur. Chemical and spectroscopic evidence is presented to show that the sulphur chain in these compounds is unbranched. The compound hitherto reported as thiocarbonyl fluoride is actually thionyl fluoride.

Bis(trifluoromethylthio)mercury with hydrogen chloride gives trifluoromethanethiol, and with chlorine gives trifluoromethanesulphenyl chloride, both in high yield. The sulphenyl chloride is obtained quantitatively by direct chlorination of bistrifluoromethyl disulphide. The properties and reactions of these compounds, and relevant ultra-violet and infra-red spectra, are discussed.

It was shown earlier that trifluoroiodomethane and sulphur react, probably by a free-radical mechanism, to give bistrifluoromethyl disulphide in high yield (Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2198, 2549). The present communication describes a more convenient route to this compound and the synthesis from it of trifluoromethanethiol and trifluoromethanesulphenyl chloride.

Carbon disulphide reacts with pure iodine pentafluoride at temperatures from 60° to 200° to give three products: bistrifluoromethyl disulphide (80%), sulphur tetrafluoride, and bistrifluoromethyl trisulphide (7%); carbon tetrafluoride is formed only at the higher temperatures. The disulphide can thus be obtained in high yield by a reaction which does not involve the relatively expensive trifluoroiodomethane. The following intermediates, which produce trifluoromethylthio-radicals, are proposed:



$$CF_3{\cdot}SI \longrightarrow CF_3{\cdot}S{\cdot} + I{\cdot}$$

$$2CF_3{\cdot}S{\cdot} \longrightarrow CF_3{\cdot}S_2{\cdot}CF_3$$

Iodine pentafluoride is a mild fluorinating agent and, if the initial attack of iodine pentafluoride on carbon disulphide removes sulphur (as the tetrafluoride), thiocarbonyl fluoride could be an intermediate which, by addition of iodine monofluoride, could yield trifluoromethanesulphenyl iodide. Iodine monofluoride has never been isolated, but evidence that it can exist in equilibrium with iodine pentafluoride will be presented later. An alternative method of formation of the sulphenyl iodide is by the intermediate formation of tri-iodosulphenyl iodide by reaction of carbon disulphide with iodine (cf. $CS_2 \xrightarrow{Cl_2} CCl_3{\cdot}SCl$), followed by replacement of iodine by fluorine (cf. $CI_4 \xrightarrow{IF_5} CF_3I$). Combination of two trifluoromethylthio-radicals would yield bistrifluoromethyl disulphide. The formation of the trisulphide involves radical reactions such as

$$CF_3{\cdot}S{\cdot} + CF_3{\cdot}S{\cdot}S{\cdot}CF_3 \longrightarrow CF_3{\cdot}S{\cdot}S{\cdot}S{\cdot}CF_3 + CF_3{\cdot}$$

or

$$2CF_3{\cdot}S{\cdot} \longrightarrow CF_3{\cdot} + CF_3{\cdot}S{\cdot}S{\cdot} \xrightarrow{CF_3{\cdot}S{\cdot}} CF_3{\cdot}S{\cdot}S{\cdot}S{\cdot}CF_3$$

Bistrifluoromethyl sulphide is not a reaction product, so that combination of a trifluoromethyl and a trifluoromethylthio-radical does not occur to any extent.

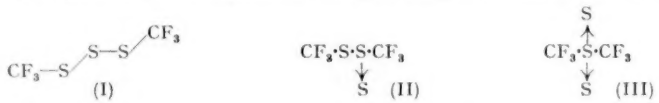
* Part X, Haszeldine, *J.*, 1953, 2075.

A report of unpublished work by Ruff (B.I.O.S. Final Report 1595, Item 22; F.I.A.T. Final Report 1114, p. 26) states that thiocarbonyl fluoride (b. p. −40°) is formed together with the compounds $C_2S_2F_6$ (b. p. −33°) and $C_3S_3F_6$ (b. p. −26°) when carbon disulphide is treated with iodine pentafluoride. The present work has shown, however, that iodine pentafluoride and carbon disulphide react only at temperatures greater than 60°, and that use of reaction temperatures up to 200° serves only to increase the rate; thiocarbonyl fluoride cannot be detected. Ruff's compound was very probably thionyl fluoride (b. p. −44°), which has sulphur and fluoride contents (37·2, 44·2%) very similar to those which would be shown by thiocarbonyl fluoride (39·0, 46·3%). Thionyl fluoride is, in fact, isolated on use of iodine pentafluoride which has been exposed to air and moisture and thus contains iodine oxytrifluoride. Sulphur tetrafluoride is produced only when the oxygen-containing compounds in the iodine pentafluoride have been destroyed.

The disulphide prepared from carbon disulphide was shown to be identical with bistrifluoromethyl disulphide, synthesised earlier from trifluoroiodomethane, by its ultra-violet and infra-red spectra, by the fact that it gave bistrifluoromethyl sulphide quantitatively on exposure to ultra-violet light, and by its reaction with mercury to give bis(trifluoromethylthio)mercury. The trisulphide (b. p. 86·5°) was shown to contain two trifluoromethyl groups by irradiation to give bistrifluoromethyl sulphide and sulphur; bistrifluoromethyl disulphide was isolated as an intermediate:

$$CF_3{\cdot}S{\cdot}S{\cdot}S{\cdot}CF_3 \xrightarrow{h\nu} CF_3{\cdot}S{\cdot}CF_3 + CF_3{\cdot}S{\cdot}S{\cdot}CF_3 \xrightarrow{h\nu} CF_3{\cdot}S{\cdot}CF_3 + S$$

The reaction of trifluoroiodomethane with sulphur is best carried out in an autoclave at 310°, since the yield of bistrifluoromethyl disulphide is then high (75%), and the formation of carbon disulphide (found as by-product when glass vessels are used, or at a temperature >320° in an autoclave) is avoided. Bistrifluoromethyl tri- and tetra-sulphides are also obtained, but not the monosulphide. Like the disulphide, both of the polysulphides are decomposed rapidly and quantitatively into fluoride, sulphide, sulphur, and carbonate when treated with aqueous sodium hydroxide. Bent (*e.g.*, I) or branched (*e.g.*, II or III) sulphur chains are possible, but two lines of evidence—the synthesis of the



(I) (II) (III)

trisulphide from trifluoromethanesulphenyl chloride and hydrogen sulphide (see below), and electron-diffraction results—show that the unbranched structure (I) is correct. It is to be expected that the tetrasulphide will have a similar structure.

The electron-diffraction results, which will be published in full by Dr. L. E. Sutton and Mr. H. Bowen, are summarised in Table 1. The S–S bond in sulphur is 2·1 Å long (Warren and Burwell, *J. Chem. Phys.*, 1935, **3**, 6; Lu and Donohue, *J. Amer. Chem. Soc.*, 1944, **67**, 818), and dimethyl trisulphide has similarly been shown to contain an unbranched sulphur chain with C–S 1·78 Å and S–S 2·04 Å (Donohue and Schomaker, *J. Chem. Phys.*, 1948, **16**, 92). That the structure of diethyl tetrasulphide involves an unbranched chain is shown by its synthesis from sulphur dichloride and ethanethiol.

TABLE 1.

| | Bond lengths (Å) | | | | | Bond lengths (Å) | | | |
|---|---|---|---|---|---|---|---|---|---|
| $(CF_3)_2X_n$ | C–F | C–X | | XĈX | $(CF_3)_2X_n$ | C–F | C–X | | XĈX |
| $(CF_3)_2S$ | $1{\cdot}32_8$ | $1{\cdot}82_8$ | — | 105·6° | $(CF_3)_2Se$ | $1{\cdot}35_6$ | $1{\cdot}95_8$ | — | 104·4° |
| $(CF_3)_2S_2$ | $1{\cdot}33_4$ | $1{\cdot}82_9$ | CŜS | 105·4 | $(CF_3)_2Se_2$ | $1{\cdot}33_6$ | $1{\cdot}93_4$ | Se–Se | $2{\cdot}33_5$ |
| | | | S–S | $2{\cdot}05_3$ | | | | | |
| $(CF_3)_2S_3$ | $1{\cdot}34_0$ | $1{\cdot}84_8$ | SŜS | 103·8 | | | | | |
| | | | S–S | $2{\cdot}06_5$ | | | | | |

The electron-diffraction results obtained with bistrifluoromethyl selenide and bistrifluoromethyl diselenide are included in Table 1 for comparison.

The ultra-violet spectra of the compounds $CF_3{\cdot}[S]_n{\cdot}CF_3$, ($n$ = 1—4) are shown in

Table 2. Since the chemical evidence for the unbranched structure for bistrifluoromethyl disulphide presented earlier (*J.*, 1952, 2198, 2549) is confirmed by electron-diffraction measurements, the shift in absorption maximum from 250 (for dialkyl disulphides) to

TABLE 2.

| | Solvent | $\lambda_{max.}$ (mμ) | $\varepsilon_{max.}$ | $\lambda_{min.}$ (mμ) | $\varepsilon_{min.}$ |
|---|---|---|---|---|---|
| $(CF_3)_2S$ | Vapour | 210 | 6·85 | — | — |
| $CF_3$·SH | Vapour | 218 | 46 | 215 | 45 |
| $(CF_3)_2S_2$ | Vapour | 235 | 290 | 212 | 110 |
| | Light petroleum | 236 | 390 | — | — |
| | Ethanol | 237 | 360 | 212 | 160 |
| $(CF_3)_2S_3$ | Vapour | 236 | 670 | 220 | 600 |
| | Ethanol | 238 | 1500 | 221 | 1330 |
| | Light petroleum | 240·5 | 1550 | 221 | 1250 |
| $(CF_3)_2S_4$ | Light petroleum | | Infl. 232—242, ε 2500 | | |
| $CF_3$·SCl | Vapour | 333 | 25 | 277 | 1·5 |
| | | 214 | 235 | — | — |
| $CCl_3$·SCl | Light petroleum | 322 | 10·0 | 293 | 6·5 |
| | $CHCl_3$ | 324 | 12·0 | 290 | 7·5 |

235 mμ in $(CF_3)_2S_m$ ($m = 2$—4) must be attributed to a decrease, caused by the fluorine atoms, in the contribution of structures of type (IV) in the excited state. The similarity of the spectra of the bistrifluoromethyl tri- and tetra-sulphide to that of the disulphide is strong evidence that the polysulphides contain unbranched chains. The slight shift to longer wave-length is attributed to additional structures involving hyperconjugation such as (V) which stabilises the excited level. For comparison $\varepsilon_{max.}$ for the tri- and tetra-

(IV) $CF_3—\overset{+}{\underset{-}{S}}\ \overset{-}{\underset{+}{S}}—CF_3$ $\qquad$ $CF_3—\overset{+}{\underset{-}{S}}\ S{=}S\ \overset{-}{\underset{+}{S}}—CF_3$ (V)

sulphides should be divided by the number of S–S bonds present; it is clear that there is a marked increase in intensity of absorption relative to that of the disulphide. The ultra-violet spectra of other polysulphides (Table 3) show that the shift in the absorption maximum to longer wave-length is much less with the fluorine compounds than with the unsubstituted compounds.

TABLE 3.

| Compound | $\lambda_{max.}$ (mμ) | $\varepsilon_{max.}$ | $\lambda_{min.}$ (mμ) | $\varepsilon_{min.}$ |
|---|---|---|---|---|
| $Et_2S_2$ [1] | 250 | 440 | 226 | 235 |
| $Et_2S_4$ [2] | | Infl. 280, ε 2700 | | |
| *cyclo*Hexyl disulphide [2] | 246 | 560 | 230 | 410 |
| *cyclo*Hexyl hexasulphide [2] | | Infl. 300, ε 7000 | | |
| Dibenzyl disulphide [3] | | Infl. 258, ε 1550 | | |
| Dibenzyl trisulphide [3] | | Infl. 272, ε 2140 | | |
| Dibenzyl tetrasulphide [3] | | Infl. 286, ε 3550 | | |

[1] Brandt *et al.*, *loc. cit.* [2] Koch, *J.*, 1949, 397. [3] Minoura, *Chem. Abs.*, 1953, **47**, 3118.

Infra-red spectroscopic evidence for the unbranched structure of bistrifluoromethyl disulphide was reported earlier (*J.*, 1952, 2549). The infra-red spectra of bistrifluoromethyl tri- and tetra-sulphide (C.S. 51 and 52 *) are very similar to that of the disulphide, with C–F stretching vibrations in the 8—9-μ region (Table 4). The band which appears at *ca.* 13·2 μ in bistrifluoromethyl mono- and di-sulphide was ascribed earlier to either the C–S stretching vibration or a $CF_3$ deformation frequency. The tri- and tetra-sulphides show a similar band (Table 4), and, since trifluoromethyl-selenium, -phosphorus (*J.*, 1953, 1565), and -arsenic (*J.*, 1953, 1552) compounds show a similar band, it is now probable that it is a deformation and not a stretching vibration. Studies on the Raman spectra of other tri- and tetra-sulphides suggest that a co-ordinate S–S double bond is not present, *i.e.*, that the chain is unbranched (Hibben, "The Raman Effect and its Chemical Applications," Reinhold Publ. Corp., New York, 1939, p. 259).

* Spectra thus designated have been deposited with the Chemical Society. Photocopies may be obtained from the General Secretary on application which must state the C.S. number.

TABLE 4.

| Compound | C–F bands (μ) | | $CF_3$ deformation (μ) | Compound | C–F bands (μ) | | $CF_3$ deformation (μ) |
|---|---|---|---|---|---|---|---|
| $(CF_3)_2S$ ... | 8·17<br>8·35<br>8·60 | 9·25 | 13·10<br>13·35 | $(CF_3)_2S_3$ | 8·50 | 9·05 | **13·24** |
| | | | | $(CF_3)_2S_4$ | 8·65 | 9·17 | **13·25** |
| $(CF_3)_2S_2$ ... | 8·43 | 9·10 | 13·12<br>13·18 | | | | |

Bis(trifluoromethylthio)mercury, prepared almost quantitatively from bistrifluoromethyl disulphide, is a valuable intermediate; from it have been synthesised trifluoromethane-thiol (infra-red spectrum, C.S. 53) and -sulphenyl chloride. The thiol (b. p. −37°; cf. MeSH, b. p. 6°) is obtained quantitatively by reaction with anhydrous hydrogen chloride:

$$CF_3{\cdot}S{\cdot}S{\cdot}CF_3 \xrightarrow{Hg,\ h\nu} (CF_3{\cdot}S)_2Hg \xrightarrow{HCl} 2CF_3{\cdot}SH + HgCl_2$$

it can be stored in a vacuum indefinitely. Its constitution follows from its method of preparation, and from its infra-red spectrum which shows the S–H stretching vibration at 3·84 μ (cf. alkanethiols, 3·72—3·90 μ), the C–F stretching bands at 8·49, 8·57, and 8·76, 8·80 μ, and the $CF_3$ deformation bands at 12·95, 13·10, 13·25 μ. The ultra-violet spectrum of the thiol (Table 2) is similar to that of bistrifluoromethyl sulphide.

Trifluoromethanethiol, the sulphur analogue of the still unknown trifluoromethanol was postulated as an intermediate in the hydrolysis by bases of bistrifluoromethyl disulphide to fluoride, carbonate, sulphide, and sulphur (*J.*, 1952, 2198):

$$CF_3{\cdot}S{\cdot}S{\cdot}CF_3 \xrightarrow{H_2O} CF_3{\cdot}SH + CF_3{\cdot}S{\cdot}OH$$

$$CF_3{\cdot}SH \xrightarrow{NaOH} F^-,\ CO_3^{--},\ S^{--}$$

$$CF_3{\cdot}S{\cdot}OH \xrightarrow{NaOH} F^-,\ CO_3^{--},\ S^{--}$$

This scheme is supported by the fact that synthetic trifluoromethanethiol is decomposed fairly slowly (12 hr.) by water with complete liberation of fluorine as fluoride, but very rapidly by aqueous sodium hydroxide; sulphur is not a reaction product from trifluoromethanethiol so that the sulphur liberated from the disulphide must be produced by further reactions of trifluoromethanesulphenic acid.

Photochemical decomposition of the thiol yields hydrogen, sulphur, fluoroform, bistrifluoromethyl sulphide, and bistrifluoromethyl disulphide, by a series of reactions clearly involving $CF_3{\cdot}S{\cdot}$ and $CF_3{\cdot}$ radicals.

Chlorine reacts with bis(trifluoromethylthio)mercury at −22°, to give the golden-yellow trifluoromethanesulphenyl chloride:

$$(CF_3{\cdot}S)_2Hg \longrightarrow 2CF_3{\cdot}SCl + HgCl_2$$

Trifluoromethylthiomercuric chloride and bistrifluoromethyl disulphide are by-products and the yield of the latter is greater at 20°. Trifluoromethylthiomercuric chloride, which is readily distinguished from bis(trifluoromethylthio)mercury by comparison of infra-red spectra (C.S. 54 and 55), is formed as follows:

$$(CF_3{\cdot}S)_2Hg + CF_3{\cdot}SCl \longrightarrow CF_3{\cdot}S{\cdot}HgCl + (CF_3)_2S_2$$

Trifluoromethanesulphenyl chloride can also be prepared directly from the disulphide by reaction with chlorine in Pyrex vessels on exposure to ultra-violet light ($CF_3{\cdot}S_2{\cdot}CF_3 \underset{}{\overset{Cl_2,\ h\nu}{\rightleftharpoons}} 2CF_3{\cdot}SCl$); this is an equilibrium reaction and the final product contains *ca.* 50% of the sulphenyl chloride. In silica reaction vessels [*i.e.*, transmitting light of wave-length >220 mμ instead of only >300 mμ (Pyrex)] extensive decomposition of the trifluoromethanesulphenyl chloride to chlorotrifluoromethane and sulphur chlorides occurs. These products are also formed when the pure sulphenyl halide is irradiated in a silica vessel.

The infra-red spectrum of the sulphenyl chloride (C.S. 56) shows the presence of the

$CF_3$ group (cf. $CCl_3$·SCl, C.S. 57), and the ultra-violet spectrum (Table 2) the presence of the S–Cl bond. The shift to the red relative to trichloromethanesulphenyl chloride (Table 2) is attributed to the contribution of structures such as $F^-CF_2{:}S{:}Cl^+$ to the excited state; comparison should also be made with sulphur dichloride ($\lambda_{max.}$ *ca.* 260 mμ, ε *ca.* 900) and sulphur monochloride ($\lambda_{max.}$ *ca.* 300 mμ, ε *ca.* 1000) (Koch, *J.*, 1949, 397).

Trifluoromethanesulphenyl chloride readily combines with mercury or with compounds which contain the S–H bond:

$$2CF_3{\cdot}SCl + Hg \longrightarrow (CF_3)_2S_2 + HgCl_2$$

$$CF_3{\cdot}SCl + CF_3{\cdot}SH \longrightarrow CF_3{\cdot}S{\cdot}S{\cdot}CF_3$$

$$CF_3{\cdot}SCl + H_2S \longrightarrow CF_3{\cdot}S{\cdot}S{\cdot}S{\cdot}CF_3$$

The last two reactions prove that the di- and tri-sulphides contain unbranched sulphur chains.

The few alkanesulphenyl halides known at present are unstable compounds. 2-Methylpropane-2-sulphenyl bromide and chloride are best prepared from the *NN*-dimethylsulphenamide (Rheinbolt and Mott, *Ber.*, 1939, **72**, 668), and trichloromethanesulphenyl chloride is best obtained by chlorination of carbon disulphide. The unstable methanesulphenyl chloride (b. p. 22°/60 mm.) has been prepared only recently by chlorination of dimethyl disulphide or of methanethiol at −15° (Schneider, *Chem. Ber.*, 1951, **84**, 911; Douglas and Brower, *J. Amer. Chem. Soc.*, 1951, **73**, 5787); reaction at higher temperatures results in attack on the alkyl groups. The fluoro-sulphenyl halides, $CF_3{\cdot}[CF_2]_n{\cdot}SCl$, are relatively stable compounds, however, and with the corresponding thiols open up a route to an extensive chemistry of perfluoroalkyl-sulphur compounds.

## Experimental

The compounds were manipulated in a conventional vacuum system fitted with mercury manometers or, for compounds which attack mercury, with spoon gauges. Molecular weights were determined by Regnault's method, and b. p.s in an isoteniscope. Unless otherwise stated, reactions were carried out in Pyrex tubes of 30—40-ml. capacity. Trifluoroiodomethane was prepared as described earlier (*J.*, 1951, 584).

*Reaction of Iodine Pentafluoride with Carbon Disulphide.*—(a) ***Under anhydrous conditions.*** Iodine pentafluoride was prepared by passing fluorine over dry iodine in a water-cooled nickel vessel until a colourless product was obtained. This was transferred to a silica apparatus and was distilled *in vacuo* immediately before use.

Iodine pentafluoride (90 g.) and carbon disulphide (10 g.) were sealed with exclusion of air in a 100-ml. autoclave and heated at 195° for 12 hr. The products were pumped from the autoclave and given a preliminary distillation by passage *in vacuo* through a trap cooled to −95°. The material which condensed in this trap was washed with water, distilled once *in vacuo* to remove water, then redistilled through a low-temperature fractionating column, to give bistrifluoromethyl disulphide (10·1 g., 76% based on carbon disulphide), b. p. 34° (Found: F, 31·5; S, 56·8%; *M*, 202. Calc. for $C_2F_6S_2$: F, 31·6; S, 56·4%; *M*, 202), and *bistrifluoromethyl trisulphide* (1·1 g., 7%), b. p. 86·4°, $n_D^{20}$ 1·4023 (Found: F, 48·9; S, 41·2%; *M*, 234. $C_2F_6S_3$ requires F, 48·7; S, 41·1%; *M*, 234). The compounds were heated at 60° for 12 hr. with 15% aqueous sodium hydroxide to cause breakdown to fluoride, sulphide, sulphur, and carbonate. For analysis an aliquot was treated with hydrogen peroxide in alkaline solution to convert sulphide and sulphur into sulphate, and the fluoride was then distilled from the acidified solution as fluorosilicic acid, which was titrated with thorium nitrate solution; a second aliquot was treated with hydrogen peroxide, acidified (hydrochloric acid), and, after removal of the fluoride by evaporation several times to dryness, sulphide was determined as barium sulphate.

Brandt, Emeléus, and Haszeldine (*loc. cit.*) report b. p. 34·6° for bistrifluoromethyl disulphide prepared from trifluoroiodomethane. The infra-red and ultra-violet spectra of the disulphides prepared by the two routes were identical. Bistrifluoromethyl trisulphide, isolated as a product of reaction of trifluoroiodomethane with sulphur, shows the same b. p. and ultra-violet and infra-red spectra as the compound described above.

The more volatile products were fractionated in a vacuum, to give carbon tetrafluoride and sulphur tetrafluoride (9·0 g., 65%, based on carbon disulphide), b. p. −38·4° (Found:

F, 69·0; S, 29·1%; *M*, 106·5. Calc. for $F_4S$: F, 70·4; S, 29·6%; *M*, 108). Fischer and Jaenckner (*Angew. Chem.*, 1929, **42**, 810) report b. p. −40° for sulphur tetrafluoride. Sulphur tetrafluoride was decomposed for analysis by 15% aqueous sodium hydroxide.

Carbon disulphide (5 g.) and iodine pentafluoride (100 g.) showed negligible reaction after 24 hr. at 20° and then 24 hr. at 50°, but after being heated at 80° for 5 days all the carbon disulphide had been converted into bistrifluoromethyl disulphide and sulphur tetrafluoride as above. Carbon tetrafluoride was not produced. Thiocarbonyl fluoride was sought at every stage but was not found.

(b) *In presence of oxygen-containing compounds.* Carbon disulphide (5 g.) was sealed with iodine pentafluoride (60 g.) which had been stored for several weeks in a steel container and had absorbed moisture. After 12 hr. at 50° the volatile reaction products were distilled, to give thionyl fluoride (2·4 g., 21%), b. p. −44° to −46° (Found: F, 44·5; S, 38·0%; *M*, 86. Calc. for $OF_2S$: F, 44·2; S, 37·2%; *M*, 86). Analysis was carried out as for sulphur tetrafluoride. Reaction of sulphuryl fluoride (0·161 g.) with water (5 ml.) in a 30-ml. tube at 20° for 12 hr. gave sulphur dioxide (0·067 g., 56%) (Found: *M*, 64. Calc. for $SO_2$: *M*, 64), identified by its infra-red spectrum.

*Reaction of Trifluoroiodomethane with Sulphur.*—Trifluoroiodomethane (45 g.) and sulphur (60 g.), heated at 310° for 36 hr. in a 300-ml. stainless-steel autoclave, gave unchanged trifluoroiodomethane (18 g., 39%) (shown by infra-red spectroscopic examination to be free from bistrifluoromethyl sulphide), bistrifluoromethyl disulphide (10·5 g., 75%), b. p. 34·5° (Found: *M*, 202. Calc. for $C_2F_6S_2$: *M*, 202), bistrifluoromethyl trisulphide (2·0 g., 12%), b. p. 86·2—86·4°, $n_D^{20}$ 1·4023 (Found: *M*, 234. Calc. for $C_2F_6S_3$: *M*, 234), *bistrifluoromethyl tetrasulphide* (0·2 g., 1%), b. p. 135°, $n_D^{20}$ 1·4608 (Found: F, 42·5; S, 48·6. $C_2F_6S_4$ requires F, 42·8; S, 48·2%), and a residue (*ca.* 0·3 g.) which probably contained higher polysulphides. The trisulphide was identical with the compound obtained from carbon disulphide as above. The tetrasulphide was completely decomposed by 15% aqueous sodium hydroxide after 15 hr. at 55°. Both the tri- and the tetra-sulphide are stable to air, water, or mercury at room temperature. The above yields of polysulphides are based on the combined products from several experiments.

*Photochemical Decomposition of Bistrifluoromethyl Trisulphide.*—The trisulphide (1·07 g.), sealed in a silica tube, was exposed to ultra-violet light for 17 days. A viscous liquid, deposited soon after irradiation started, was slowly converted into rhombic sulphur (0·289 g., 66%). Fractionation of the volatile products gave bistrifluoromethyl sulphide (0·384 g., 49%) (*M*, 170), identified spectroscopically, bistrifluoromethyl disulphide (0·313 g., 34%) (*M*, 202), and an unidentified fraction (0·061 g.) (Found: *M*, 89). The disulphide was sealed in a 10-ml. silica tube and irradiation was continued for 5 days, to give unchanged disulphide (0·021 g.) (Found: *M*, 199) and bistrifluoromethyl sulphide (0·163 g., 62%). The total yield of the monosulphide is 70%.

*Reaction of Bis(trifluoromethylthio)mercury with Hydrogen Chloride.*—The mercurial was prepared by the irradiation for 4 days of bistrifluoromethyl disulphide (5·0 g.) and mercury (80 g.) in a vigorously shaken 100-ml. silica tube. The residual bistrifluoromethyl disulphide (4%) and the small amount of bistrifluoromethyl sulphide formed (5%) were removed, and the solid products were extracted with ether. Evaporation of the dried ($P_2O_5$) ethereal extracts at room temperature in a dried atmosphere gave the pure mercurial (90%), m. p. 37—38°. Anhydrous hydrogen chloride was purified in a vacuum system.

Bis(trifluoromethylthio)mercury (1·05 g.) and anhydrous hydrogen chloride (0·228 g.) were sealed in a 30-ml. Pyrex tube. An immediate reaction was apparent as the tube warmed to room temperature, and the mercurial was converted into a white amorphous powder (mercuric chloride). After 48 hr. the volatile products were distilled, to give *trifluoromethanethiol* (0·53 g., 99%), b. p. −36·7° (Found: F, 56·0; S, 31·7%; *M*, 102. $CHF_3S$ requires F, 55·9; S, 31·4%; *M*, 102), and unchanged hydrogen chloride (22%). Trifluoromethanethiol was completely decomposed to fluoride, sulphide, and carbonate by 15% aqueous sodium hydroxide at 20° in 6 hr.

*Photochemical or Hydrolytic Decomposition of Trifluoromethanethiol.*—The thiol (0·4844 g.), sealed in a silica tube and exposed to ultra-violet light for 10 days, gave hydrogen (0·0019 g., 40%) (Found: *M*, 2), unchanged trifluoromethanethiol (0·0323 g., 7%), fluoroform (0·1489 g., 44%) (Found: *M*, 70. Calc. for $CHF_3$: *M*, 70) identified by its infra-red spectrum, bistrifluoromethyl sulphide (0·0161 g., 4%) (Found: *M*, 167. Calc. for $C_2F_6S$: *M*, 170) identified by its infra-red spectrum, bistrifluoromethyl disulphide (0·2057 g., 43%) (Found: *M*, 202. Calc. for $C_2F_6S_2$: *M*, 202), and sulphur (0·0618 g., 41%). The unchanged trifluoromethane-

thiol and bistrifluoromethyl sulphide were obtained as a mixture from which the thiol was removed by treatment at 70° for 24 hr. with 15% aqueous sodium hydroxide.

Trifluoromethanethiol (0·131 g.) was sealed with water (2 ml.) in a 10-ml. Carius tube, and allowed to warm to room temperature. As soon as the ice melted, fumes were evolved and a yellow oil was formed. This had disappeared after 12 hr. at room temperature. The aqueous solution was made alkaline and treated with an excess of hydrogen peroxide, and the fluoride was determined as described above (Found : F, 54·8. Calc. for $CHF_3S$ : F, 55·9%).

*Preparation of Trifluoromethanesulphenyl Chloride.*—(a) *From bis(trifluoromethylthio)mercury.* In a typical reaction the mercurial (4·99 g.) and dry chlorine (1·60 g.) were condensed into a Carius tube which was sealed and allowed to warm to −22°. An immediate reaction was apparent and the crystalline mercurial changed into a white amorphous powder. After 3 hr. the volatile products were distilled in a vacuum, to give bistrifluoromethyl disulphide (0·29 g., 11%) and *trifluoromethanesulphenyl chloride* (2·44 g., 72%), b. p. −0·7° (Found : Cl, 25·9; F, 41·7; S, 23·1%; *M*, 137. $CClF_3S$ requires Cl, 26·0; F, 41·8; S, 23·4%; *M*, 136·5). The last compound was decomposed by sodium fusion for analysis. When treated with 15% sodium hydroxide, trifluoromethanesulphenyl chloride liberated its chlorine quantitatively as chloride, but not all its fluorine as fluoride. The following vapour pressures have been recorded for the sulphenyl chloride, which condenses to a golden-yellow liquid : −25·1°, 262·2 mm.; −21·3°, 316·0 mm.; −17·3°, 379·4 mm.; −13·7°, 446·0 mm.; −3·3°, 684·4 mm.; −1·3°, 740·2 mm.

Reaction of chlorine (0·37 g.) with the mercurial (1·13 g.) at room temperature for 4 days gave bistrifluoromethyl disulphide (0·301 g., 60%) (Found : *M*, 202) and a correspondingly lower yield of trifluoromethanesulphenyl chloride.

The solid product from the first reaction above was extracted with ether; evaporation of the ether followed by fractional sublimation gave *trifluoromethylthiomercuric chloride* (Found : Cl, 11·6. $CClF_3SHg$ requires Cl, 10·5%), slightly contaminated with mercuric chloride. Attempts to separate the mercurial from mercuric chloride by differential solvent extraction failed.

(b) *From bistrifluoromethyl disulphide and chlorine.* The disulphide (10·0 g.) and dry chlorine (10·0 g.) were sealed in a 100-ml. Pyrex Carius tube and exposed to ultra-violet light for 14 days. Distillation gave unchanged disulphide (45%) (Found : *M*, 203), chlorine (Found : *M*, 71), and trifluoromethanesulphenyl chloride (100%) (Found : *M*, 138).

When irradiated in a 100-ml. silica tube for 10 days, bistrifluoromethyl disulphide (1·51 g.) and chlorine (0·80 g.) gave unchanged chlorine (0·11 g., 14%), trifluoromethanesulphenyl chloride (0·94 g., 46%), chlorotrifluoromethane (0·50 g., 32%) (Found : *M*, 105. Calc. for $CClF_3$ : *M*, 104·5), disulphur dichloride (0·20 g.), and a mixture of unchanged bistrifluoromethyl disulphide and sulphur dichloride. This mixture was treated with water and redistilled, to give bistrifluoromethyl disulphide (0·17 g., 11%) (Found : *M*, 200).

*Reactions of Trifluoromethanesulphenyl Chloride.*—(a) *With mercury.* The chloro-compound (0·52 g.), shaken with mercury (10 g.) at room temperature for 4 hr., gave bistrifluoromethyl disulphide (0·37 g., 96%), identified by its molecular weight (202) and vapour pressure.

(b) *With trifluoromethanethiol.* The sulphenyl halide (0·29 g.) and trifluoromethanethiol (0·23 g.) were sealed in a Carius tube and set aside for 14 days. The now colourless liquid was distilled to give hydrogen chloride and bistrifluoromethyl disulphide (0·429 g., 94%) (Found : *M*, 202).

(c) *With hydrogen sulphide.* Hydrogen sulphide (0·171 g.) and trifluoromethanesulphenyl chloride (0·75 g.) reacted slowly (1 month) with disappearance of the yellow colour, to give bistrifluoromethyl trisulphide (0·57 g., 92%), b. p. 87°, $n_D^{20}$ 1·4020 (Found : *M*, 233. Calc. for $C_2F_6S_3$ : *M*, 234), identical with the material described earlier.

(d) *Photolysis.* Trifluoromethanesulphenyl chloride (0·789 g.) was exposed to ultra-violet light in a silica tube for 14 days, to give sulphur (0·136 g., 73%), chlorotrifluoromethane (0·419 g., 69%) (Found: *M*, 104), and liquid products ($S_2Cl_2$, $SCl_2$, $CF_3{\cdot}S_2{\cdot}CF_3$) which were not examined further.

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## 640. *Polarographic Behaviour of Disubstituted Benzenes: Relation of $E_{\frac{1}{2}}$'s to Electron Densities and Activation Energies for Electrophilic Substitution.*

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The polarographic half-wave potentials ($E_{\frac{1}{2}}$) of a number of substituted nitrobenzenes, benzaldehydes, and iodobenzenes have been measured under comparable conditions, and have been correlated with (*a*) electron densities in *o*-, *m*-, and *p*-positions, and (*b*) polarization energies defining the orientating properties of substituents. General agreement was found, and some notable exceptions, *e.g.*, $E_{\frac{1}{2}}$'s for *ortho*-compounds, have been explained by hydrogen-bonding (chelation). The high *para*-yields for anionoid ($-E$) substituents are predicted exceedingly well by $E_{\frac{1}{2}}$ results.

We have investigated the polarographic reduction of a number of *o*-, *m*-, and *p*-disubstituted benzenes, and found variations in the reduction potential ($E_{\frac{1}{2}}$) in each series of *o*-, *m*-, and *p*-derivatives, which appeared to be related to certain properties of the molecule and to the influence one substituent had on the other, one of the substituents being the reducible group. We have already shown (*J.*, 1951, 13) that, whereas the reduction potential of iodobenzene is −1·650 v (compared with the standard calomel electrode), the $E_{\frac{1}{2}}$'s of *o*-, *m*-, and *p*-iodotoluene are respectively −1·683, −1·660, and −1·685 v. As in every case it is the iodo-group which is being reduced, we assume that the methyl group *o*- or *p*- to the iodine makes the reduction more difficult. This behaviour is explicable if we consider those cases where the methyl group shows its favourable influences on electrophilic substitution in positions *ortho* and *para* to it. Evidently the reduction is the very reverse of this, and involves the *addition* of an electron to the reducible group, and so the methyl group opposes this in the *o*- and the *p*-position.

Although the mechanism of reduction varies a little from molecule to molecule in the number of electrons finally involved, and sometimes shows dependence on the pH of the medium and sometimes does not, we believe in the correctness of our basic assumption, namely, that the relevant step in the process is the addition of an electron to the molecule and that $E_{\frac{1}{2}}$ is a measure of the energy required for this addition. Whether the electron goes into the next higher orbital of the ring itself or into an orbital of the reducible group is not directly ascertainable from any of our results. But $E_{\frac{1}{2}}$ must be proportional to the activation energy necessary to overcome some potential barrier.

Our results might therefore be expected to show some relation (*a*) to electron densities at positions in the ring *ortho*, *meta*, and *para* to some group (Pauling and Wheland, *J. Amer. Chem. Soc.*, 1935, **57**, 2086; Ploquin, *Mem. Soc. Chim. France*, 1948, 640), or (*b*) to activation energies for substitution of hydrogen in the ring by the reducible group (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; Dewar, *J.*, 1949, 463).

(*a*) Calculations of electron densities in disubstituted benzenes are very difficult, and only approximations can be obtained. In comparing our results with such data, we are aware that we are concerned mainly with differences, and that a constant quantity, the electronic property of the reducible group itself, appears in the calculations in a form modified by the *o*-, *m*-, or *p*-substituent. It seems reasonable therefore to use electron-density data obtained for the single, modifying substituents (Pauling and Wheland, *loc. cit.*).

Differences in $E_{\frac{1}{2}}$ for *o*-, *m*-, and *p*-derivatives can be equated, where possible, to differences in electron densities in the *o*-, *m*-, and *p*-positions.

(*b*) In the theoretical treatment initiated by Wheland (*loc. cit.*) and refined by Dewar (*loc. cit.*) the relevant part of the activation energy required for electrophilic substitution is identified with the $\pi$ electron-energy difference between XPh and the transition complex XPh Y, in other words, with the energy needed to provide an unshared pair of electrons at the point of attack. Dewar has calculated the electron energies for the three types of substituted benzenes: pure inductive, $I$; anionoid, $-E$; cationoid, $+E$, with varying $\delta_x$ values ($\delta_x$ being a parameter, positive or negative in sign, which measures the electro-

negativity or electropositivity of the substituted atom or group in relation to the carbon atom in benzene). The results of his calculations, represented diagrammatically in his paper, account for *o–p* ratios in reaction yields, and also suggest that the activation energy for any electronic type of substituted benzene can exceed the activation energy for benzene itself (as is required for *deactivating* substituents), provided that a sufficiently high, positive $\theta$ is assigned to the substituents.

We have tabulated our results under headings corresponding to the different electronic types of substituent. Where $E_{\frac{1}{2}}$ varies with the pH, we have quoted our results under the varying pH conditions. We have selected the low pH region for comparison, because this is the region where $E_{\frac{1}{2}}$–pH curves of substituted and unsubstituted compounds are approximately parallel and show no complication due to change of mechanism, dissociation equilibria, etc. Comparisons are further possible only when other factors such as the medium, ionic strength, etc., are kept constant, and for these reasons we have had to repeat some of the earlier measurements so as to bring them into line with our own results.

TABLE 1. *Influence of the methyl group ($E_{\frac{1}{2}}$ in* V).

| *Reduction of* $NO_2$ | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 3·16 |
|---|---|---|---|---|
| $PhNO_2$ | 0·935 | 0·326 | 0·366 | 0·430 |
| *o*-$C_6H_4Me{\cdot}NO_2$ | 1·005 | 0·358 | 0·390 | 0·525 |
| *m*-$C_6H_4Me{\cdot}NO_2$ | 0·936 | 0·305 | 0·338 | 0·416 |
| *p*-$C_6H_4Me{\cdot}NO_2$ | 1·035 | 0·336 | 0·366 | 0·442 |

| *Reduction of* CHO | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 2·59 | 3·16 |
|---|---|---|---|---|---|
| Ph·CHO | 1·506 | 1·000 | 1·022 | 1·051 | 1·088 |
| *o*-$C_6H_4Me{\cdot}CHO$ | 1·493 | 0·962 | 0·990 | 1·018 | 1·062 |
| *m*-$C_6H_4Me{\cdot}CHO$ | 1·526 | 1·000 | 1·030 | 1·056 | 1·092 |
| *p*-$C_6H_4Me{\cdot}CHO$ | 1·562 | 1·020 | 1·050 | 1·080 | 1·106 |

| *Reduction of* I | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | *Reduction of* I | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ |
|---|---|---|---|
| PhI | 1·650 | *m*-$C_6H_4MeI$ | 1·660 |
| *o*-$C_6H_4MeI$ | 1·683 | *p*-$C_6H_4MeI$ | 1·685 |

*Influence of the Methyl Group.*—The methyl group is considered to be an anionoid inductive ($-I$) substituent in Dewar's treatment (*loc. cit.*). It is known to activate the benzene ring for second substitution and to be *op*-orientating. Experiment shows that it leads to a greater degree of *o*-nitration than of *o*-halogenation. Yields (%) obtained by Holleman (*Chem. Reviews*, 1925, **1**, 187) for nitration and bromination of toluene were :

| | *ortho* | *meta* | *para* | | *ortho* | *meta* | *para* |
|---|---|---|---|---|---|---|---|
| Nitration | 56 | 3·1 | 40·9 | Bromination | 39·7 | — | 60·3 |

The $E_{\frac{1}{2}}$'s of the *o*- and *p*-methyl compounds are more negative than those of the otherwise unsubstituted compounds, in agreement with the *ortho-para*-activating effect of the methyl group. We notice further that $E_{\frac{1}{2}}$ of *o*-nitrotoluene is more negative than that of *p*-nitrotoluene, whereas *o*- and *p*-iodotoluene have almost equal $E_{\frac{1}{2}}$. Formylation of toluene yields mainly *p*-tolualdehyde, and $E_{\frac{1}{2}}$ of this is also the most negative of the aldehyde series; but the very low $E_{\frac{1}{2}}$ observed for the reduction of *o*-tolualdehyde could be the consequence of some hydrogen-bonding between the aldehyde and the *o*-methyl group.

We tried to apply the electron-density calculations of Pauling and Wheland (*loc. cit.*) for inductive substituents. The following equations are given for the electron densities :

$$Q_x = (1 + 0{\cdot}398\delta_1 - 0{\cdot}315\delta_2)e$$

$$Q_{ortho} = (1 - 0{\cdot}158\delta_1 - 0{\cdot}407\delta_2)e$$

$$Q_{meta} = (1 + 0{\cdot}0093\delta_1 - 0{\cdot}259\delta_2)e$$

$$Q_{para} = (1 - 0{\cdot}1028\delta_1 + 0{\cdot}019\delta_2)e$$

The reduction potentials (v) of the iodotoluenes in relation to iodobenzene are :

| | $E_{\frac{1}{2}}$ | Relative to PhI | | $E_{\frac{1}{2}}$ | Relative to PhI |
|---|---|---|---|---|---|
| Iodobenzene | −1·650 | | *m*-Iodotoluene | −1·660 | −0·011 |
| *o*-Iodotoluene | −1·683 | −0·033 | *p*-Iodotoluene | −1·685 | −0·035 |

If we take the electron density of the unsubstituted iodobenzene to be unity, the differences in $E_{\frac{1}{2}}$ may be considered to be the electron-density differences caused by the substituent in the iodotoluenes:

$$Q_{ortho} = (1 + 0{\cdot}033)e = (1 - 0{\cdot}158\delta_1 + 0{\cdot}407\delta_2)e$$

$$Q_{meta} = (1 + 0{\cdot}011)e = (1 + 0{\cdot}0093\delta_1 - 0{\cdot}259\delta_2)e$$

from which $\delta_1 = -0{\cdot}352$ and $\delta_2 = -0{\cdot}055$.

Substituting these values in the equation for $Q_{para}$, we obtain for $Q_{para} = (1 + 0{\cdot}035)e$ in agreement with the experimental results.

In Dewar's treatment for (*I*) substituents, the activation energy for negative $\delta_x$ values show the decreasing order which corresponds to the increasing order of $E_{\frac{1}{2}}$'s, Unsubst. > *meta* > *para* > *ortho*; the greater the spread, the more negative is $\delta_x$.

The polarographic $E_{\frac{1}{2}}$'s follow this order, but the methyl group must be assigned a more negative $\delta_x$ value in conjunction with the nitro-group than with the iodo-group in order to account for its effect on $E_{\frac{1}{2}}$ of the *o*-nitro-group being more pronounced than that on $E_{\frac{1}{2}}$ of the *o*-iodo-group. As the parameter $\delta_x$ stands for the electron affinity of the group relative to the electron affinity of the benzene-carbon atom, the numerical value of the negative $\delta_x$ is the measure of its electron-releasing power. It is not unreasonable to account for it as such, and to assume that it should release electrons more readily in presence of the very electronegative nitro-group than in presence of the less electronegative iodo-group.

We can see that the polarographic results can be brought into agreement with both the electron-density and polarization-energy treatments. This is not astonishing, as it is known (Sandorfy, Vroeland, Yvan, Chalvet, and Daudel, *Mem. Soc. Chim. France*, 1950, 304) that the two kinds of treatment lead to very similar conclusions for inductive substituents.

*Influence of* —E *Substituents.*—Nitration is directed by all —*E* substituents to a greater extent in the *p*- than in the *o*-position, the $\frac{1}{2}o$–$p$ ratios (Dewar, *loc. cit.*) never exceeding unity. This ratio increases in the series Cl, Br, I. The $\frac{1}{2}o$–$p$ ratio of the nitrodiphenyls is highest of all (0·56). A similar trend can be observed when these substituents affect $E_{\frac{1}{2}}$ of the nitro-group. $E_{\frac{1}{2}}$ of the nitro-group *para* to the activating methoxy-, amino,- and hydroxy-groups is more negative than $E_{\frac{1}{2}}$ for unsubstituted nitrobenzene, and also more negative than $E_{\frac{1}{2}}$ for the *ortho*-disposition, in agreement with the low $\frac{1}{2}o$–$p$ ratios.

The activating substituents hardly affect $E_{\frac{1}{2}}$ when they are *meta* to the reducible group, but $E_{\frac{1}{2}}$ of *o*-nitrophenol is less negative than that of *m*-nitrophenol, in spite of the *ortho*-yields, being higher than the *meta*-yields when phenol is nitrated.

The deactivating halogens,* and also the phenyl group, lower $E_{\frac{1}{2}}$ of the $NO_2$ reduction in all positions, but most for the *meta*-position, in agreement with their *op*-directing properties. The increasing $\frac{1}{2}o$–$p$ ratios (Dewar, *loc. cit.*) in the series Cl, Br, I are reflected in the $E_{\frac{1}{2}}$'s: $p < o$ for iodo- and bromo-nitrobenzene, but $o < p$ for the chloronitrobenzenes. $E_{\frac{1}{2}}$ of 2-nitrodiphenyl is more negative than that of the 4-isomer, in accord with their relatively high $\frac{1}{2}o$–$p$ ratio.

The overall $E_{\frac{1}{2}}$-lowering produced by the halogens is in the order Cl < Br < I, the reverse of the order of their deactivating influence.

Direct introduction of the CHO group into the substituted benzene ring, when it can be done, and into diphenyl, by the Gattermann–Koch reaction, yield *para*-products exclusively. The $E_{\frac{1}{2}}$'s of all *para*-substituted benzaldehydes are the most negative.

Iodination of aniline, halogeno-benzenes, and diphenyl yield *para*-products almost exclusively, but a large amount of *o*-iodophenol is obtained. The $E_{\frac{1}{2}}$'s of all —*E* substituted iodobenzenes are in the order $o < m < p$. Hydroxy- and amino-groups when *para* to iodine make its reduction more difficult than it is in iodobenzene.

The lower $E_{\frac{1}{2}}$'s of the *o*-halogeno-iodobenzenes and benzaldehydes, compared with the

* The oft-quoted statement that iodobenzene is nitrated more readily than benzene is surely incorrect. We have repeated the experiment, by a method similar to that of Ingold and Bird (*J.*, 1938, 918), using the polarographic method to estimate the nitrobenzene (NB) and iodonitrobenzene formed (INB) and have found the ratio of the yields INB/NB to be 0·17—0·22.

*m*-isomers, seem to be in contradiction to the orientating properties of the halogens in their reactions, the *o*-isomer generally being formed in second largest quantities. It must be remembered that halogenations and formylation have to be carried out in the presence of catalysts, and the ratio of isomers formed is influenced by the catalyst. For instance,

TABLE 2. *Anionoid* (−E) *substituents* ($E_{\frac{1}{2}}$ *in* v).

(*a*) *Reduction of* $NO_2$.

| | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 3·16 | | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 3·16 |
|---|---|---|---|---|---|---|---|---|---|
| Ph·$NO_2$ | 0·935 | 0·326 | 0·366 | 0·430 | *o*-$NO_2$·$C_6H_4$·OH | 0·990 | 0·246 | 0·284 | 0·362 |
| *o*-$C_6H_4I$·$NO_2$ | 0·816 | 0·204 | 0·232 | 0·306 | *m*-$NO_2$·$C_6H_4$·OH | 0·960 | 0·310 | 0·350 | 0·418 |
| *m*-$C_6H_4I$·$NO_2$ | 0·757 | 0·176 | 0·214 | 0·276 | *p*-$NO_2$·$C_6H_4$·OH | 1·350 | 0·408 | 0·470 | 0·566 |
| *p*-$C_6H_4I$·$NO_2$ | 0·780 | 0·194 | 0·226 | 0·294 | *o*-$NO_2$·$C_6H_4$·$NH_2$ | 1·030 | 0·372 | 0·422 | 0·488 |
| *o*-$C_6H_4Br$·$NO_2$ | 0·860 | 0·263 | 0·294 | 0·396 | *m*-$NO_2$·$C_6H_4$·$NH_2$ | 0·935 | 0·320 | 0·356 | 0·422 |
| *m*-$C_6H_4Br$·$NO_2$ | 0·816 | 0·208 | 0·238 | 0·308 | *p*-$NO_2$·$C_6H_4$·$NH_2$ | 1·128 | 0·438 | 0·476 | 0·554 |
| *p*-$C_6H_4Br$·$NO_2$ | 0·854 | 0·230 | 0·270 | 0·342 | *o*-$C_6H_4Ph$·$NO_2$ | 0·928 | 0·290 | 0·341 | 0·412 |
| *o*-$C_6H_4Cl$·$NO_2$ | 0·866 | 0·256 | 0·306 | 0·410 | *m*-$C_6H_4Ph$·$NO_2$ | 0·844 | 0·228 | 0·264 | 0·348 |
| *m*-$C_6H_4Cl$·$NO_2$ | 0·830 | 0·222 | 0·262 | 0·340 | *p*-$C_6H_4Ph$·$NO_2$ | 0·854 | 0·228 | 0·266 | 0·342 |
| *p*-$C_6H_4Cl$·$NO_2$ | 0·930 | 0·292 | 0·332 | 0·400 | | | | | |

(*b*) *Reduction of* CHO *group.*

| | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 2·59 | 3·16 | | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH: 1·73 | 2·25 | 2·59 | 3·16 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph·CHO | 1·506 | 1·000 | 1·022 | 1·051 | 1·088 | *o*-MeO·$C_6H_4$·CHO | 1·494 | 0·960 | 0·994 | 1·020 | — |
| *o*-$C_6H_4I$·CHO | 1·248 | 0·827 | 0·850 | 0·876 | 0·914 | *m*-MeO·$C_6H_4$·CHO | 1·622 | 1·080 | 1·106 | 1·122 | — |
| *m*-$C_6H_4I$·CHO | 1·390 | 0·860 | 0·888 | 0·912 | 0·952 | *o*-HO·$C_6H_4$·CHO | 1·504 | 1·050 | 1·070 | 1·098 | 1·134 |
| *p*-$C_6H_4I$·CHO | 1·400 | 0·878 | 0·912 | 0·934 | 0·980 | *m*-HO·$C_6H_4$·CHO | 1·500 | 1·008 | 1·030 | 1·053 | 1·098 |
| *m*-$C_6H_4Br$·CHO | 1·358 | 0·904 | 0·948 | 0·986 | 1·028 | *p*-HO·$C_6H_4$·CHO | 1·72 | 1·116 | 1·146 | 1·166 | 1·200 |
| *p*-$C_6H_4Br$·CHO | 1·410 | 0·918 | 0·952 | 0·992 | 1·032 | *o*-$NH_2$·$C_6H_4$·CHO | — | — | 1·030 | — | 1·090 |
| *o*-$C_6H_4Cl$·CHO | 1·331 | 0·868 | 0·895 | 0·918 | 0·970 | *m*-$NH_2$·$C_6H_4$·CHO | 1·52 | 0·950 | 0·974 | — | 1·030 |
| *m*-$C_6H_4Cl$·CHO | 1·384 | 0·910 | 0·950 | 0·982 | 1·030 | *p*-$NH_2$·$C_6H_4$·CHO | 1·70 | 1·064 | — | — | 1·158 |
| *p*-$C_6H_4Cl$·CHO | 1·422 | 0·952 | 0·976 | 1·006 | 1·050 | | | | | | |

(*c*) *Reduction of iodo-group in* $C_6H_4R$·I *in aq.* $NEt_4Br$ ($E_{\frac{1}{2}}$ *for* PhI = 1·65).

| R | *o*- | *m*- | *p*- | R | *o*- | *m*- | *p*- | R | *o*- | *m*- | *p*- |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 1·235 | 1·38 | 1·46 | Br | 1·30 | 1·43 | 1·53 | Cl | 1·34 | 1·45 | 1·54 |
| HO | 1·49 | 1·62 | 1·685 | $NH_2$ | 1·56 | 1·66 | 1·72 | | | | |
| *o*-$C_6H_4$PhI | 1·48 | | | *m*-$C_6H_4$PhI | 1·56 | | | *p*-$C_6H_4$PhI | 1·585 | | |

(*d*) *Relation between* $E_{\frac{1}{2}}$ *and activation* (*polarization*) *energies* (*Dewar*).

| Substituent | Reducible group | Relative $E_{\frac{1}{2}}$ | Estimated $\delta_s$ | Relative activation energies for $\delta_s$ |
|---|---|---|---|---|
| $NH_2$ | $NO_2$ | *m*≪unsubst.<*o*<*p* | 1·3 | *m*>unsubst.>*o*>*p* |
| | CHO | *m*<unsubst.<*o*<*p* | 1·4 | *m*>unsubst.>*o*>*p* |
| | I | *o*<unsubst.<*m*<*p* | 1·7 | *m*>*o*>unsubst.>*p* |
| HO | $NO_2$ | *o*<*m*<unsubst.<*p* | 1·5 (?) | *m*>*o*>unsubst.>*p* |
| | CHO | unsubst.≪*m*<*o*<*p* | 1·4 | *m*>unsubst.>*o*>*p* |
| | I | *o*<*m*<unsubst.<*p* | 1·7 | *m*>*o*>unsubst.>*p* |
| Ph | $NO_2$ | *m*≪*p*<*o*<unsubst. | 1·8 | *m*>*o*>*p*>unsubst. |
| | I | *o*<*m*<*p*<unsubst. | 2·2 | *o*>*m*>*p*>unsubst. |
| Cl | $NO_2$ | *m*<*p*<*o*<unsubst. | 1·8 | *m*>*o*>*p*>unsubst. |
| | CHO | *o*<*m*<*p*<unsubst. | 2·2 | *o*>*m*>*p*>unsubst. |
| | I | *o*<*m*<*p*<unsubst. | 2·3 | *o*>*m*>*p*>unsubst. |
| Br | $NO_2$ | *m*<*p*<*o*<unsubst. | 1·9 | *m*>*o*>*p*>unsubst. |
| | CHO | *m*<*p*<unsubst. | 2·2 | *m*>*p*>unsubst. |
| | I | *o*<*m*<*p*<unsubst. | 2·3 | *o*>*m*>*p*>unsubst. |
| I | $NO_2$ | *m*<*p*<*o*<unsubst. | 2·0 | *m*>*o*>*p*>unsubst. |
| | CHO | *o*<*m*<*p*<unsubst. | 2·3 | *o*>*m*>*p*>unsubst. |
| | I | *o*<*m*<*p*<unsubst. | 2·4 | *o*>*m*>*p*>unsubst. |

The iodo-phenols and -anilines have $E_{\frac{1}{2}}$'s dependent on pH; the order of ease of reduction is, however, the same as in aq. $NEt_4Br$ over the whole pH scale, apart from the very alkaline pH regions where the phenolic hydroxyl group is dissociated.

bromination of bromobenzene at 55° with aluminium chloride as carrier gives 8·3% of *ortho*-, 30·1% of *meta*-, and 61·6% of *para*-isomer (Richter, "Text-Book of Organic Chemistry," 1951, p. 408, John Wiley and Sons, Inc., New York), this order being in agreement with the $E_{\frac{1}{2}}$'s.

The most striking exception to the general parallel between electrophilic substitution and polarographic reduction is the part played by the *o*-hydroxy-group. The $E_{\frac{1}{2}}$'s of *o*-nitro- and *o*-iodo-phenol are the lowest among the isomers, whilst the yields of *ortho*-isomers on nitration and iodination of phenol are fairly high. This is probably caused by hydrogen-bonding of the nitro-group and iodine atom with the *o*-hydroxy-group, which could be responsible for the unexpectedly low $E_{\frac{1}{2}}$'s and perhaps account for the high *ortho*-yields (de la Mare, *J.*, 1949, 2871).

Polarographic results do not agree with calculations of electron densities in the positions *ortho*, *meta*, and *para* to $-E$ substituents, as these calculations lead either to unity in the case of the *meta*-position (Sandorfy, Vroelant, *et al.*, *locc. cit.*) or to highest electron densities in the *ortho*-positions, exceeding unity even for the halogens (Jaffé, *J. Chem. Phys.*, 1952, **20**, 279). The $E_{\frac{1}{2}}$'s, however, do follow the trend indicated by Dewar's polarization-energy calculations for isomeric substituted benzenes (*loc. cit.*).

We have listed in Table 2*d* the $\delta_x$ values by means of which the calculated polarization energies for the substituted benzenes and for benzene (2·54 β) follow best the opposite order of the $E_{\frac{1}{2}}$'s. It will be noticed that the value of $\delta_x$ which allows this agreement varies with each substituent in its relation to the reducible group in the molecule. The shift is in the *same sense* as that already shown with respect to the methyl group, *i.e.*, the positive $\delta_x$ is *smaller* when the substituent affects the more electronegative nitro-group than when it affects the less electronegative CHO and iodo-group.

The parallel would be better still if the calculated polarization energies for the *meta*-positions were somewhat lower for all $\delta_x$ values, a requirement indicated by other experimental evidence and best summarized in the negative sign of Hammett's σ value for the *m*-amino-group.

The order of electronegativity of $-E$ substituents from their effect on $E_{\frac{1}{2}}$ would be $NH_2 < OH < OMe < Ph < Cl < Br < I$.

*Influence of* +E *Substituents.*—+*E* Substituents deactivate the benzene ring for a second substitution. They cause nitration to occur mainly in the *meta*-position, but sometimes fairly high yields of *ortho*-compounds are obtained, *e.g.*, *o*-nitrobenzoic acid (18·5%) and ethyl *o*-nitrobenzoate (28·3%) (Hollemann, *loc. cit.*). Yields of *para*-compounds are always the lowest.

TABLE 3. *Cationoid* (+E) *substituents. Reduction of* $NO_2$.

| | $E_{\frac{1}{2}}$ in aq. $NEt_4Br$ | $E_{\frac{1}{2}}$ in buffers of pH : 1·73 | 2·25 | 3·16 |
|---|---|---|---|---|
| $Ph{\cdot}NO_2$ ..... | 0·935 | 0·326 | 0·366 | 0·430 |
| $o\text{-}C_6H_4(NO_2)_2$ ..... | 0·570 [1] | 0·134 [1] | 0·168 [1] | 0·230 [1] |
| $m\text{-}C_6H_4(NO_2)_2$ ... | 0·684 | 0·145 | 0·187 | 0·266 |
| $p\text{-}C_6H_4(NO_2)_2$ ... | 0·436 | 0·082 | 0·102 | 0·158 |
| $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CHO$ | 0·690 [2] | 0·228 [2] | 0·286 [2] | 0·346 [2] |
| $m\text{-}NO_2{\cdot}C_6H_4{\cdot}CHO$ | 0·822 | 0·257 | 0·296 | 0·380 |
| $p\text{-}NO_2{\cdot}C_6H_4CHO$ | 0·632 | 0·174 | 0·220 | 0·322 |
| $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2Et$ | 0·826 | 0·282 | 0·313 | 0·400 |
| $m\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2Et$ | 0·850 | 0·214 | 0·264 | 0·330 |
| $p\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2Et$ | 0·770 | 0·166 | 0·200 | 0·282 |
| $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2H$ | 0·526 [3] / 0·968 | 0·304 | 0·340 | 0·420 |
| $m\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2H$ | 0·440 / 1·026 | 0·252 | 0·294 | 0·362 |
| $p\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2H$ | 0·390 / 0·972 | 0·186 | 0·226 | 0·304 |

[1] $E_{\frac{1}{2}}$'s of the reduction of the second nitro-group are equal to the $E_{\frac{1}{2}}$'s of the nitroanilines listed in Table 2*a*. [2] $E_{\frac{1}{2}}$'s of the aldehyde group are equal to $E_{\frac{1}{2}}$'s of the amino-aldehydes listed in Table 2*b*. [3] Two waves appear with the unbuffered solutions, believed to be due to reduction of the nitrobenzoic acid molecule and of the nitrobenzoate ion.

$E_{\frac{1}{2}}$ of the nitro-group is lowered by these substituents in all positions. For dinitrobenzenes and nitrobenzaldehydes $E_{\frac{1}{2}}$ follows the order $p < o < m <$ unsubst., which agrees with the orientating effect of nitro- and CHO-groups, but for the nitrobenzoic acids and ethyl nitrobenzoates the order is $p < m < o <$ unsubst. This should indicate highest yields for the *ortho*-compounds; steric hindrance might account for their being low.

The influence of the nitro-group on the polarographic reduction of CHO and iodo-substituents could not be studied as reduction of the nitro-group occurred at a potential lower than that required for reduction of the other two. Nor, for the same reason, could the influence of the CHO group on the reduction of the iodo-group be observed.

Relative values for $E_{\frac{1}{2}}$ for the iodobenzoic acids ($o < m < p <$ unsubst.) (*J.*, 1951,

3502) cannot be compared with results for the iodination of benzoic acid, as the last reaction does not occur at low temperatures. However, bromination of benzoic acid with potassium bromate and hydrogen bromide at 70—80° yields mainly *p*-bromobenzoic acid (Claus and Reh, *Annalen*, 1891, **266**, 206), whereas large yields of *meta*-compounds are generally obtained at high temperatures.

The polarization energies for $+E$ substituents (Dewar, *loc. cit.*) show the order $p > o > m >$ unsubst. for positive $\delta_x$ values up to 2·3, and are in the opposite order to the $E_{\frac{1}{2}}$'s of the isomers of dinitrobenzene and nitrobenzaldehyde. But no such parallel is found with the ethyl nitrobenzoates, nitrobenzoic acids, and iodobenzoic acids. Should the polarization energies required for *meta*-substitution be somewhat higher for all $\delta_x$ values, the agreement would be preserved with $\delta_x = 1$—1·3 for the nitrobenzoic acids and ethyl nitrobenzoates and with $\delta_x = 2{\cdot}5$ for the iodobenzoic acids. $\delta_x$ for CHO would then be about 1·5 and for $NO_2$ about 1·8, as the overall lowering of $E_{\frac{1}{2}}$ by the substituents shows the order $CO_2H < CO_2Et < CHO < NO_2$, and their electronegativities should increase in the same order. The $\delta_x$ that has to be assigned to the carboxyl group when associated with an iodo-substituent is again higher than the $\delta_x$ assigned when it is associated with a nitro-group.

We tried to substitute $E_{\frac{1}{2}}$ differences into the Pauling–Wheland formulæ for *inductive* substituents (as described for the iodotoluenes) in the case of the ethyl nitrobenzoates and the nitrobenzoic acids ($E_{\frac{1}{2}}$ values of Page, Smith, and Waller at pH 4 were used; *J. Phys. Chem.*, 1949, **53**, 545), and for both series of compounds agreement was obtained, *i.e.*, $\delta_1$ and $\delta_2$ values obtained from two equations and substituted into the third equation lead to the observed $E_{\frac{1}{2}}$ difference. Values obtained for the nitrobenzoic acids are $\delta_1 = +1{\cdot}13$ and $\delta_2 = +0{\cdot}36$, and for ethyl nitrobenzoates $\delta_1 = +1{\cdot}33$ and $\delta_2 = +0{\cdot}36$.

This procedure is not completely justified, as the Pauling–Wheland equations account for the inductive effect of the substituents only, and the agreement might be a coincidence. It is interesting, however, that the calculated $\delta_2$ values are close to $\frac{1}{3}\delta_1$ in both instances, as has proved most satisfactory for calculations (Dewar and Jaffé, *locc. cit.*), and that the calculated $\delta_1$ values, +1·13 for the carboxy-group and +1·33 for the ethoxycarbonyl group are approximately those which follow from the Dewar diagrams.

*Influence of the Nitrogen Atom in Pyridine.*—The nitrogen atom deactivates the pyridine ring strongly towards substitution. It favours nitration and sulphonation in the *meta*-position; halogenations have to be carried out at high temperatures, and a number of multisubstituted by-products including 2 : 3- and 2 : 5-halogenopyridines are generally obtained together with the *meta*(3)-product. Direct iodination of pyridine yields an addition product rather than a substitution product.

The iodopyridines have $E_{\frac{1}{2}}$ as follows: 2-, 1·418 v; 3-, 1·387 v; 4-, 1·348 v ($E_{\frac{1}{2}}$ for PhI is 1·650 v). These values suggest that direct iodination of pyridine, if it could be achieved, would occur at position 2 (equivalent to the *ortho*-positions).

No similar order of polarization energies can be found in Dewar's diagram for inductive substituents. It is interesting, however, that this order of $E_{\frac{1}{2}}$'s is similar to the $E_{\frac{1}{2}}$ order of the *misbehaving* $+E$ substituents when affecting the reduction of the nitro-group.

Insofar as this argument has significance, the pyridine-nitrogen atom, the carboxy-group, and the ethoxycarbonyl group would be of the same electronic type.

## Experimental

The polarographic apparatus was a manually controlled three-electrode set up as described by Lingane and Kolthoff (*J. Amer. Chem. Soc.*, 1939, **61**, 825).

Buffers were made from sodium acetate, hydrochloric acid, and potassium chloride to 0·2N, in 60% alcohol. The pH was measured with a glass electrode on a Leeds and Northrup pH-meter, model 7663-AI, and controlled on a more accurate hand-made apparatus kindly supplied by Mr. H. J. Gardner. 0·01M-Tetraethylammonium bromide was made from the Eastman Kodak product; the solution contained 66% of alcohol.

The polarographic measurements were carried out at 25·0° ± 0·1°, the temperature being controlled by a thermostat. The solutions were M/3100 with respect to the reducible compound. Potentials were measured against the saturated calomel electrode.

Materials were obtained from our store or prepared by well-known methods and were purified by recrystallization, vacuum-sublimation, or distillation to constant m. p. or b. p. respectively.

*Preparation of Iodo-compounds not described elsewhere.*—*3-Iododiphenyl.* 3-Aminodiphenyl was diazotized in hydrochloric acid at 5° and treated with potassium iodide. The 3-iododiphenyl was extracted with ether from alkaline solution and, after evaporation of the solvent and recrystallization three times from 50% ethanol, was colourless and had m. p. 25° (Found: C, 51·2; H, 3·5. Calc. for $C_{12}H_9I$: C, 51·45; H, 3·2%).

*3-Iodopyridine.* This was prepared from 3-aminopyridine as described above. Recrystallized from 50% ethanol it had m. p. 52° (Found: C, 29·2; H, 2·0. Calc. for $C_5H_4NI$: C, 29·3; H, 1·95%).

*4-Iodopyridine.* Small quantities (about 15% yield) of 4-iodopyridine could be prepared as follows. 4-Aminopyridine (2 g.), dissolved in acetic acid (15 c.c.), concentrated sulphuric acid (1·5 c.c.), and water (2 c.c.), was diazotized ($NaNO_2$) at 0° and potassium iodide (excess) added. The mixture was kept at room temperature for a day, then heated on a water-bath of 50° for ½ hr. The solution was made alkaline and the product was extracted with ether. After evaporation of the solvent and recrystallization from 50% ethanol, 4-iodopyridine had m. p. 100° (decomp.) (Found: N, 6·7. Calc. for $C_5H_4NI$: N, 6·8%).

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## 641. *Reaction of Nitric Oxide with Gaseous Hydrocarbon Free Radicals. Part I.* iso*Propyl Radical.*

By H. T. J. CHILTON and B. G. GOWENLOCK.

The reaction products of the pyrolysis of di*iso*propylmercury in a flow system with nitrogen and nitric oxide as carrier gas have been studied. Absorption spectra and chemical tests show that acetoxime and a nitroso-compound are formed. Various physical properties of the mixture have been studied and are discussed in relation to the monomeric and dimeric states of nitroso-compounds and isomerization of the nitroso-compound to the acetoxime.

THE inhibiting effect of nitric oxide on radical chain reactions in the decomposition of certain organic compounds has been summarised by Hinshelwood ("Kinetics of Chemical Change," Oxford Univ. Press, 1940, p. 92). It is suggested that the reaction $R + NO \longrightarrow R{\cdot}NO$ takes place, where R is a free radical. Nitroso-compounds have never been isolated in nitric oxide-inhibited reactions involving gaseous hydrocarbon free radicals, although they are formed in the reaction of nitric oxide in solution with triphenylmethyl (Schlenk and Mair, *Ber.*, 1911, **44**, 1170), diphenylnitrogen (Wieland, *Annalen*, 1911, **381**, 200), triphenylhydrazyl (Goldschmidt, *Ber.*, 1920, **53**, 44), and diphenylnitric oxide (Wieland and Offenbächer, *ibid.*, 1914, **47**, 2111). It is to be noted that the radical αα-diphenyl-β-trinitrophenylhydrazyl and that from 9-chloro-10-hydroxyphenanthrene do not react with nitric oxide in solution (Goldschmidt and co-workers, *Ber.*, 1922, **55**, 628; *Annalen*, 1924, **438**, 202; 1925, **445**, 123). It has been assumed that nitroso-compounds formed in gaseous reactions are decomposed according to such mechanisms as

$$CH_3{\cdot}NO \longrightarrow H_2C{:}N{\cdot}OH \longrightarrow HCN + H_2O$$

The evidence concerning the decomposition products of nitroso-compounds is summarised in Table 1. It will be seen that the mechanism cited is not unambiguously supported. It is, however, established that formaldoxime decomposes to give hydrogen cyanide and water (H. A. Taylor and Bender, *J. Chem. Phys.*, 1941, **9**, 761), the products interacting to give principally carbon monoxide and ammonia, together with some nitrogen, hydrogen, ethane, and traces of an unsaturated hydrocarbon. The rate of reaction of methyl radicals with nitric oxide has been measured by Durham and Steacie (*ibid.*, 1952, **20**, 582), who give no details about any products of the reaction.

Nitroso-paraffins are difficult to prepare by normal chemical methods, only *tert.*-nitroso-aliphatic compounds having been so prepared. Nitroso-paraffins are colourless crystalline dimeric compounds in the solid state, dissociated by heat or dissolution to the intensely blue monomeric compound. Halogenonitroso-paraffins such as 2-chloro- and 2-bromo-2-nitrosopropane exist as the blue monomers, whereas those that have secondary hydrogen

TABLE 1. *Products from nitric oxide-inhibited decompositions.*

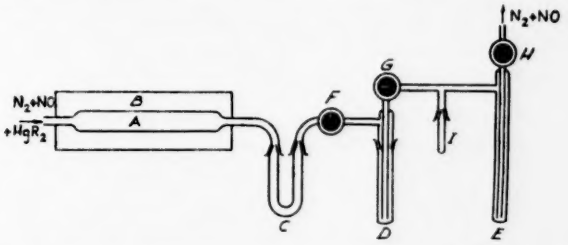
| Organic compound | Product | Ref. | Remarks |
|---|---|---|---|
| $C_2H_6$ | Trace of cyanide | *a* | Thermal decomposition |
| $Bu^nOMe$ | Trace of cyanide | *b* | |
| $Me_2O$ | $NH_3$. Blue product at $-180°$ | *c* | |
| $Et_2O$ | $Me{\cdot}NH_2$ | *c* | |
| $Me_2Hg$ | Unidentified white solid | *d* | Photochemical decomposition |
| $CF_3I$ | Deep blue solid at $-180°$ | *e* | |

(*a*) Küchler and Theile, *Z. physikal. Chem.*, 1939, **42**, *B*, 359. (*b*) Magram and H. A. Taylor, *J. Chem. Phys.*, 1941, **9**, 760. (*c*) Meissner and Thompson, *Nature*, 1937, **139**, 1018. (*d*) Thompson and Linnett, *Trans. Faraday Soc.*, 1937, **33**, 874. (*e*) Dacey, *Discuss. Faraday Soc.*, 1953, **14**, 84.

atoms, *e.g.*, 1-chloro-1-nitrosoethane, rapidly dimerise and isomerise to the corresponding oxime. Nitrosomethane has been prepared by the photolysis of *tert.*-butyl nitrite (Coe and Doumani, *J. Amer. Chem. Soc.*, 1948, **70**, 1516), its properties being similar to those of other nitroso-paraffins apart from the fact that isomerization to formaldoxime is slow.

## EXPERIMENTAL

The apparatus was a modification of that used by Butler and Polanyi (*Trans. Faraday Soc.*, 1943, **39**, 19) and the relevant section of it is illustrated in the Figure. The carrier gas, a mixture




of nitrogen and nitric oxide in approximately equal amounts and at a total pressure of about 3·7 mm., picked up di*iso*propylmercury at a pressure of about 0·1 mm. by means of the trap system devised by Warhurst (*ibid*, 1939, **35**, 674) and passed through the reaction vessel *A* heated by the furnace *B*. The pyrolyses were performed in the temperature range 230—280°. The products were condensed out in the U-tube *C* and the traps *D* and *E*, which were cooled to $-78°$, $-130°$, and $-183°$, respectively. Nitric oxide was used up (presumably owing to reaction with *iso*propyl radicals), and therefore it was added throughout the experiment, the pressure in *A* being kept constant to within $\pm 0·2$ mm. Nitrogen was made by heating sodium azide in a high vacuum. Nitric oxide was prepared by Rees (M.Sc. Thesis, Wales, 1925) according to Winkler's method (*Ber.*, 1901, **34**, 1408), and intensively purified. It was still colourless, and some was passed through a solid carbon dioxide–acetone trap, frozen in liquid air, and the white solid allowed to evaporate slowly, the gas being collected in an evacuated bulb. Di*iso*propylmercury was prepared according to Marvel and Gould's method (*J. Amer. Chem. Soc.*, 1922, **44**, 153) as modified by Gilman and Brown (*ibid.*, 1930, **52**, 3314): it was fractionally distilled in high vacuum and further distilled to constant vapour pressure within the Warhurst trap system. Except during runs, it was kept at $-78°$ under high vacuum; under such conditions it survives for considerable periods without decomposition. On the completion of a run, the traps were examined: the U-tube *C* contained a thin film of mercury and some di*iso*propylmercury, the trap *D* contained a yellow solid and a liquid (mainly $C_6$ hydrocarbons with a little di*iso*propylmercury), and the trap *E* contained a small amount of a yellow solid together with $C_3$ hydrocarbons. Air was admitted into the section containing *A* and *C*, up to trap *F*, and *C* was detached, allowed to warm to room temperature, and washed

out with ether. The washings were pale blue, the colour rapidly fading. The section between traps *F* and *H* was evacuated with the low-temperature baths in position, and then the taps *G* and *H* were closed. It was observed on removing the liquid-oxygen bath from *E* that the small amount of yellow solid condensed on the walls of the trap melted and then formed a white solid. The m. p. of the yellow solid on the walls of trap *D* was therefore estimated approximately. The trap was cooled by a pentane bath in an evacuable unsilvered Dewar vessel that was cooled by liquid oxygen. The liquid oxygen was removed, and the pentane bath allowed to warm slowly. A chromel–alumel thermocouple in a thin glass tube was inserted into the pentane so that the junction of the thermocouple was approximately at the central point of the yellow deposit. As the bath warmed, the deposit was observed, the temperature readings being made simultaneously. The deposit melts within the range $-78°$ to $-85°$ to a yellow-brown liquid which speedily changes into a white solid. The pentane bath was then removed, the tap *G* opened, and liquid oxygen placed around the tube *I*, whereupon all remaining products other than the white solid distilled over into *I*.

*Experiments with the White Solid.*—A detailed investigation of the white solid was made. It was a white waxy substance, the lower part of the deposit in trap *D* having a leaf-like structure. It had a camphor-like smell and a sharp bitter odour, and was fairly volatile. When kept for a few hours, the white solid changed to colourless crystals, some needle-shaped and others minute square plates. The m. p. varied between 40° and 59° according to the run. In one case the solid melted between 44° and 47°, softening taking place about 37°. Close examination during the m. p. determination by the capillary tube method showed that there were two types of crystal present, one melting to a colourless liquid, and the other to a blue liquid the colour of which rapidly faded at the m. p. Further heating to about 90° caused bubbling to take place, and at about 95° the liquid became green. On cooling, the liquid decolorized, and when it was reheated to 95° the green colour reappeared. This process was continually repeated. In another case the m. p. was 52°, and the green colour appeared at about 85° whereat boiling also took place.

The behaviour of the solid in various solvents was investigated, and the appearance of colours on dissolving, on gentle warming, and on boiling was noted. The colour that appeared on dissolution faded completely, the rate of disappearance varying considerably with the solvent. Chloroform and bromoform were the only solvents in which the colour that appeared on gentle warming could not be regenerated by cooling and further gentle heating. The colour that appeared on boiling disappeared on cooling and could be regenerated by boiling except for the dioxan solution where a yellow-green colour remained on cooling. The results are given in Table 2.

TABLE 2.*

| | | | Colour of solution on: | | | | | | Colour of solution on: | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Solvent | B. p. | ε | dissolving | gentle heating | boiling | Solvent | B. p. | ε | dissolving | gentle heating | boiling |
| $n$-$C_5H_{12}$ ... | 36° | 1·85 | (Insoluble) | | | $CH_3{\cdot}CO_2H$ | 118° | 6·13 | — | B | B |
| $n$-$C_6H_{14}$ ... | 69 | 1·91 | (Insoluble) | | | $CH_3{\cdot}CO_2Me$ | 51 | 8·02 | — | B | — |
| $CCl_4$ ..... | 77 | 2·22 | — | — | — | $H{\cdot}CO_2Me$... | 32 | 8·37 | — | — | — |
| Dioxan ... | 101 | 2·24 | B | G | G | $CH_2Cl_2$..... | 40 | 9·14 | — | B | — |
| $C_6H_6$ ..... | 80 | 2·30 | B | — | pale B | $COMe_2$ ... | 56 | 21·45 | — | — | — |
| PhMe ..... | 111 | 2·38 | B | — | B | EtOH ..... | 78 | 25·80 | — | — | — |
| $Et_2O$ ..... | 35 | 4·36 | B | — | — | $Pr^nNO_2$ ... | 131 | ~30 | — | B | B |
| $CHCl_3$ ..... | 61 | 4·64 | B | B | — | $CH_3{\cdot}CN$ ... | 82 | 37·5 | — | B | — |
| $CHBr_3$ ... | 150 | 4·73 | B | B | — | $H_2O$ ..... | 100 | 80 | — | — | — |
| $CH_3{\cdot}CO_2Et$ | 77 | 6·11 | B | — | — | | | | | | |

* B. p. of solvent given to nearest degree, dielectric constant (ε) to two decimal places. Values taken from Weissberger and Proskauer ("Organic Solvents," Oxford Univ. Press, 1935); B = blue, G = green. Solid is soluble in all but the first two solvents listed.

Chemical tests were made for the presence of nitroso- and oxime groups according to Feigl's method ("Spot Tests," Elsevier, Amsterdam, 1939). The Liebermann nitroso-test (*idem, ibid.*, p. 267) gave a green colour, the product becoming green-yellow in sodium hydroxide solution. The oxime test (*idem, ibid.*, p. 291) gave a pink colour and when the solid was fused with diphenylamine, and concentrated sulphuric acid added, a faint pale blue colour resulted (Coe and Doumani, *loc. cit.*).

Investigations of the ultra-violet absorption spectra of solutions of the solid were made with a Unicam S.P. 500 photoelectric quartz spectrophotometer. As the composition of the

substance was unknown, only the data for $\lambda_{max.}$ in dilute solutions are presented, no determination of $\varepsilon$ values being made. The values obtained are given in Tables 3 (aqueous solutions) and 4 (ethereal solutions), literature data being taken from Braude (*Ann. Reports*, 1945, **42**, 112). It is to be noted that the $\lambda_{max.}$ values are the same for Pyrex, silica, and silicon-coated traps (trap *D* in Fig. 1) and also for the product when a packed reaction vessel (increase in surface/volume ratio by factor of 11) is used.

TABLE 3.

| Substance | $\lambda_{max.}$ (mμ) | Substance | $\lambda_{max.}$ (mμ) |
|---|---|---|---|
| Solid (Pyrex trap) | <200, 266 | Acetoxime | <200 |
| Solid + HCl (Pyrex trap) | <200, 266 | Acetoxime (Braude) | 190 |

A specimen of the solid was sealed off under vacuum in a small Pyrex tube and kept in the dark. The solid changed from its usual white, waxy appearance to colourless moist square crystals, which sublimed within the tube. Examination with a high-powered lens showed no differences in appearance between these crystals and acetoxime. After some time some of the crystals disappeared and a pale yellow oil was formed. The yellow oil sometimes became a yellow-white wax that melted to a yellow oil when the tube was warmed with the hand. The tube was opened after 10 weeks, the cutting being made so as to separate the portion containing the crystals from that containing the oil. The crystals had no detectable odour, gave no colour in ether, melted at 57—60° (m. p. of acetoxime 59°), and gave no colour change on further heating. They were readily soluble in cold water, and in ethereal solution absorption maxima were found at 209—210 and 289—291 mμ (small peak). The oil dissolved in ether with no coloration and gave absorption maxima at 289—291 and 209 mμ (small peak). On warming, the oil became green at about 94° and boiled at about 145°, leaving a water-soluble white solid on cooling. Reference to Table 4 shows that a partial separation of acetoxime and a nitroso-compound has been made by sealing off *in vacuo*.

Solutions of the solid in ether and ethyl alcohol were kept in corked tubes for about 6 weeks. Spectroscopic examination then showed absorption maxima at 208 mμ (ether) and 206 and 285—290 mμ (alcohol), the second peak for the alcoholic solution being very small. Reference to Table 4 shows that the nitroso-compound has disappeared in ethereal solution and almost disappeared in alcoholic solution.

TABLE 4.

| Substance | $\lambda_{max.}$ (mμ) | Substance | $\lambda_{max.}$ (mμ) |
|---|---|---|---|
| Solid (Pyrex trap) | 211, 292, 665 * | Di*iso*propylmercury | 218 |
| ,, (silica trap) | 211, 289—291 | Washings of U-tube | 218—220, 290 |
| ,, (silicone-coated trap) | 207, 290—291 | Acetoxime | 210—212 |
| ,, (packed reaction vessel) | 209, 289 | Nitroso-compound (Braude) | 300, 665 |

* Only taken for Pyrex trap; weak absorption, colour fades during determination.

## DISCUSSION

The product is evidently a mixture of acetoxime and a nitroso-compound, probably 2-nitrosopropane. We suggest the following mechanism to account for these results, the *iso*propyl radicals being produced by dissociation of the Hg–C bonds.

$$Me_2CH + NO \longrightarrow Me_2CH{\cdot}NO \quad (1)$$

$$Me_2CH{\cdot}NO \longrightarrow Me_2C{:}NOH \quad (2)$$

$$2Me_2CH{\cdot}NO \longrightarrow \text{Dimer} \quad (3)$$

$$2Me_2CH \longrightarrow Me_2CH{\cdot}CHMe_2 \quad (4)$$

$$2Me_2CH \longrightarrow C_3H_8 + C_3H_6 \quad (5)$$

Reaction (2) may occur in the gaseous phase, at the wall of the reaction vessel, or at the trap surface. As neither alteration of the trap surface nor packing of the reaction vessel produces any significant change in the nature of the white solid, it is probable that reaction (2) is a gas-phase isomerization reaction. From the reaction conditions, it is probable that reaction (2) has an activation energy in the range of 30—40 kcal./mole. This isomerization reaction can also take place slowly in non-aqueous solution at room

temperature, but is not accelerated in aqueous solution by hydrochloric acid, again suggesting a non-ionic mechanism of isomerization. The variation of the m. p. of the white solid is due to the varying proportions of the two constituents present. It is probable from comparison with previous work (see p. 3233) that the blue liquid obtained in m. p. experiments is the 2-nitrosopropane monomer whereas the yellow-white solid melting to a pale oil in the sealed tube experiment is the dimer (contaminated with a small amount of acetoxime). We can tentatively assign a m. p. of about 15—25° to the dimer and a b. p. of about 145° to the monomer, the monomer–dimer transition taking place in the region 85—95°. The melting and transition of the yellow solid at −78° to −85° to a yellow-brown liquid and then a white solid may be associated either with the change 2-nitrosopropane monomer (solid) ⟶ 2-nitrosopropane monomer (liquid) ⟶ 2-nitrosopropane (dimer, solid) as suggested by us in a preliminary communication (*Nature*, 1953, **172**, 73), or may be due to acetoxime monomer (solid) ⟶ acetoxime monomer (liquid) ⟶ acetoxime trimer (solid). The colour of the solid as a thin film on the inside of a glass tube was seen by reflected light, and the difference between this colour and the blue or green colour in transmitted light usually associated with monomeric nitroso-compounds may be due to these conditions.

The behaviour of the solid when dissolved in various solvents requires correlation. The simplest feature is that of colour change on boiling. We suggest that it is almost solely a temperature effect, the blue coloration only occurring for solvents whose b. p. is above 80°. However, bromoform, acetonitrile, and water do not give this blue colour. The colour change on solution is given only for those solvents with dielectric constants in the range 2·24—6·11. Although such a correlation may be fortuitous, we suggest that it is too well marked to be disregarded, as the solvents concerned have singularly few other features in common. It must also be noted that from ether to dioxan the blue colour fades with increasing rapidity. The production of the blue colour on gentle warming is difficult of explanation. It seems that the scheme proposed by Coe and Doumani (*loc. cit.*) for nitrosomethane, generalised as

$$\underset{\text{colourless}}{(RNO)_2} \rightleftharpoons \underset{\text{blue}}{2RNO}$$

is unable to account for all these variations or even for all their observations, for they record a blue colour above the m. p. of the dimer (122°) and a blue colour on heating in toluene (b. p. 110°). It is necessary that solvation states must be considered in any explanation of these data. We reserve further comments until parallel observations are available for other nitroso-compounds.

The general failure to isolate nitroso-paraffins in nitric oxide-inhibited reactions is probably due to the decomposition of these compounds under the usual conditions associated with pyrolysis by the static method. The short time of reaction associated with the flow method, together with the lower temperatures necessary to break the relatively weak Hg–C bonds (Gowenlock J. C. Polanyi, and Warhurst, *Proc. Roy. Soc.*, 1953, *A*, **218**, 269; Chilton and Gowenlock, to be published) compared with C–C and C–O bonds, favour the isolation of the nitroso-compound.

One of us (H. T. J. C.) thanks the Swansea Local Education Authority for a post-graduate award, and one (B. G. G.) thanks the Chemical Society for a grant. We also thank Midland Silicones Ltd. for a sample of MS 200/350 silicone fluid, and Professor C. W. Shoppee for helpful discussions.

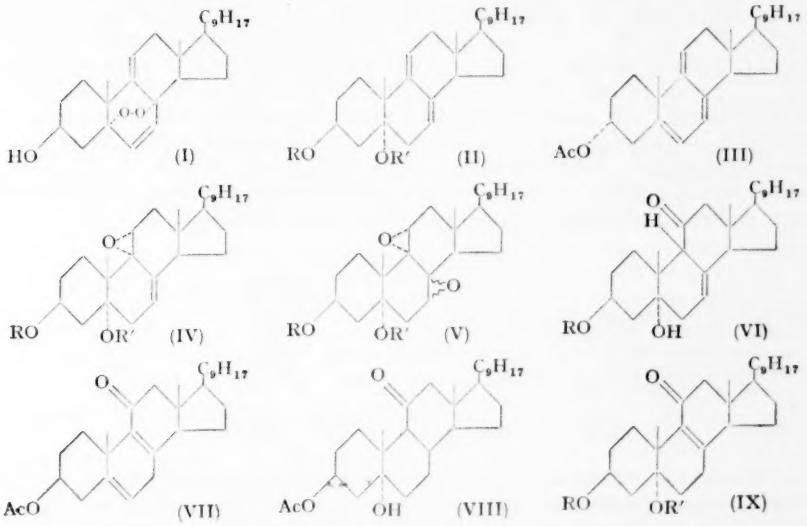
UNIVERSITY COLLEGE, SWANSEA. [*Received, May 19th*, 1953.]

## 642. *Studies on the Epoxides of 5α-Hydroxy- and 5α-Acetoxy-$\Delta^{7:9}$-steroids.*

By D. C. Burke, J. H. Turnbull, and Walter Wilson.

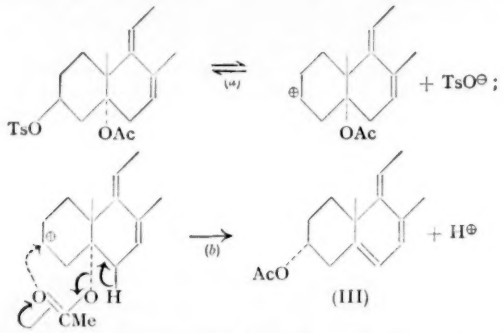
Ergosta-7 : 9 : 22-triene-3β : 5α-diol and its acetates have been converted into the 9α : 11α-monoepoxides. The α-configuration of the 5-hydroxyl group in this series is confirmed by the transformation of 5α-acetoxyergosta-7 : 9 : 22-trien-3β-yl toluene-*p*-sulphonate into *epi*dehydroergosteryl acetate. The mechanism of this reaction is discussed. Acid or alkali treatment of 3β-acetoxy-5-α-hydroxy-9β-ergosta-7 : 22-dien-11-one, obtained by boron trifluoride rearrangement of the 3-acetoxy-5-hydroxy-epoxide, gives a variety of products, including the $\Delta^{8(9)}$-ketone. Reduction of the latter with lithium in liquid ammonia yields 3β-acetoxy-5α-hydroxyergost-22-en-11-one, a valuable potential intermediate for cortisone synthesis. Mineral acid transforms the epoxides into $\Delta^{8(9)}$-7 : 11-diols, then into $\Delta^{9}$-7-ketones. The latter subsequently isomerise to $\Delta^{8(9)}$-ketones, and the 5-substitutent, particularly an acetoxy-group, may be eliminated.

The conversion of ergosterol into cortisone, through dehydroergosterol 5 : 8-epidioxide (I), has been envisaged by E. R. H. Jones and his collaborators (*J.*, 1952, 4883, 4890, 4894; 1953, 2921), who have converted the 7 : 9 : 22-triene alcohol (II; R = R′ = H), obtained by reducing the epidioxide, into 11-keto-steroids by epoxidation reactions similar to those previously described by Swiss and American workers (for references, see Jones *et al.*, *loc. cit.*; Birch, *Ann. Reports*, 1951, **48**, 204). We also have studied the formation and reactions of epoxides of 5-hydroxy- and 5-acetoxy-7 : 9 : 22-trienes.




The 5-hydroxyl group in the triene (II; R = R′ = H) had been assigned the α-configuration, because it can be acetylated (although with difficulty) (Jones *et al.*, *J.*, 1952, 4883). This configuration has been confirmed by means of a reaction discovered by Plattner and Lang (*Helv. Chim. Acta*, 1944, **27**, 1872; Shoppee, *Ann. Reports*, 1946, **43**, 212) : the 5-acetoxytrienyl 3-toluene-*p*-sulphonate (II; R = *p*-$C_6H_4$·$SO_2$, R′ = Ac) when refluxed in pyridine afforded a 70% yield of 3α-acetoxyergosta-5 : 7 : 9 : 22-tetraene (*epi*dehydroergosteryl acetate) (III), recognised by the 5 : 7 : 9-triene absorption band at 325 mμ and by hydrolysis to the 3α-hydroxy-steroid which gave no precipitate with

digitonin (cf. *Chem. and Ind.*, 1953, 317). The rate of formation of (III) under different conditions was followed spectroscopically. The reaction proceeded readily in boiling pyridine, but was markedly inhibited by addition of toluene-*p*-sulphonic acid or sodium acetate. When allowance was made for the auto-inhibitory effect of toluene-*p*-sulphonic acid, first-order kinetics were observed. These observations indicate the mechanism illustrated; the rate-determining step is (*b*) and is relatively slow; added acetate ions could compete for the carbonium ions, and thereby inhibit reaction (*b*).




Monoepoxides were obtained in 40—90% yields from the trienediol (II; R = R′ = H) and its acetates with permonophthalic or perbenzoic acid in ether or benzene. Media containing chloroform were unsatisfactory, as strong acid impurities (cf. Kolthoff, Lee, and Mairs, *J. Polymer. Sci.*, 1947, **2**, 199) rearranged some of each epoxide into 7-ketones (see below). The trien-5-ol (II; R = Ac, R′ = H) and monoperphthalic acid in ether–chloroform gave a complex mixture from which two 7-ketones (XI*A*; R = Ac, R′ = H; and XII; R = Ac, R′ = H) were isolated. From a reaction in ether–benzene, the main product (60%) was the monoepoxide (IV; R = Ac, R′ = H); some diepoxide (3%) (V; R = Ac, R′ = H) and a second unconjugated 7-ketone (3%) (XI*B*; R = Ac, R′ = H) were also obtained. The reactions (discussed later) of the monoepoxides are similar to those of other $\Delta^7$-9α : 11α-epoxides reported recently. The structural parallelism of these compounds is confirmed by the fairly uniform large decrease (Δ) in molecular rotation which occurs when a 7 : 9-diene is converted into the monoepoxide (see Table) (cf. Henner, Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936).

*Molecular rotations.*

| | Steroid | 9α : 11a-Epoxide | Δ |
|---|---|---|---|
| Ergosta-7 : 9 : 22-triene-3β : 5α-diol [1] | +198° | − 17° | −215° |
| 3β-Acetoxyergosta-7 : 9 : 22-trien-5α-ol [1] | +218 | + 19 | −200 |
| 5α-Acetoxyergosta-7 : 9 : 22-trien-3β-ol [1] | +395 | +205 | −190 |
| 5β : 5α-Diacetoxyergosta-7 : 9 : 22-triene [1] | +471 | +256 | −215 |
| Ergosta-7 : 9 : 22-trien-3β-ol [2] | + 83 | −140 | −223 |

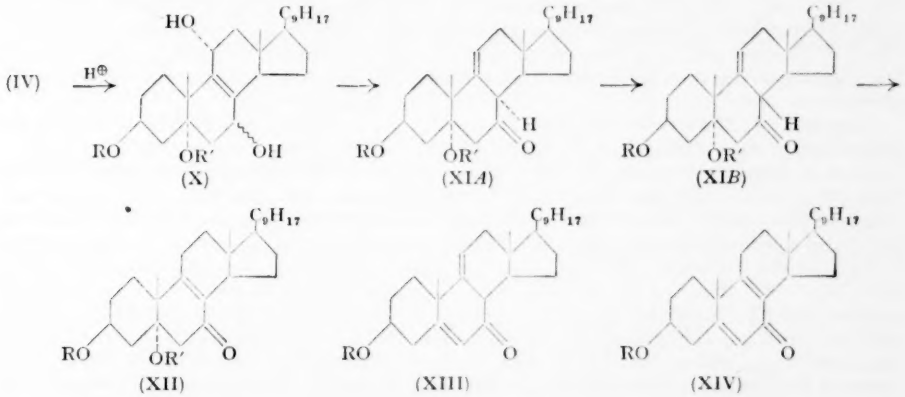
[1] Present work. [2] Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696.

The diepoxides isolated as by-products from some of these reactions are probably the 7 : 8-9α : 11α-compounds; the alternative keto-epoxide structure is excluded by the stability of the compounds to alkali, whilst the retention of the side-chain double bond is indicated by the nature of the absorption near to 200 mμ (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737).

Probably for steric reasons, the $\Delta^7$-9 : 11-epoxide system is stable to alkali. In contrast, mineral acids very rapidly produce 7-ketones by allylic rearrangements, whilst boron trifluoride yields 11-ketones. Jones *et al.* (*J.*, 1953, 2921; also Heusler and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 398) recently showed that 7 : 8-unsaturated 9β-11-ketones are the primary products in the latter reaction. 3β-Acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (VI; R = Ac) was made by Jones's method; a substance

$C_{30}H_{44}O_3$, probably (VII), was separated in 14% yield from the crude product by chromatography. The stability of the 9β-ketone (VI; R = Ac) to alumina is noteworthy, as rapid conversion into the 9α-isomer occurs in the analogous 5-hydrogen series (Jones *et al.*, *J.*, 1953, 2921). The Manchester workers isomerised (VI; R = Ac) to the conjugated ketone (IX; R = Ac, R′ = H), using zinc and acetic acid. We have studied the use of mineral acids and alkalis as catalysts in this isomerisation; in addition to compounds (IX), several by-products were obtained, which are being examined further.

The difficult reduction of the ditertiary double bond in $\Delta^{8(9)}$11-ketones has been accomplished by use of lithium in liquid ammonia (Schoenewaldt *et al.*, *loc. cit.*; Sondheimer, Yashin, Mancera, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2696; Heusler, Heusser, and Anliker, *Helv. Chim. Acta*, 1953, **36**, 652); the products have the normal (8β : 9α-)configuration. Reduction of the ketone (IX; R = Ac, R′ = H) with this reagent gave 3β-acetoxy-5α-hydroxyergost-22-en-11-one (VIII), which is a valuable intermediate for cortisone synthesis.




The conversion of Δ⁷-9 : 11-epoxides into 7-ketones by mineral acids has recently become well known (cf., *e.g.*, Heusser, Eichenberger, Kurath, Dallenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Schoenewaldt *et al.*, *loc. cit.*; Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892). The products obtained in the present experiments are probably formed in the sequence (IV) ⟶ (X) ⟶ (XI*A*) ⟶ (XI*B*) ⟶ (XII). These reactions appear to be slower in the 5α-acetoxy- than in the 5α-hydroxy-series (cf. Jones *et al.*, *J.*, 1953, 2921). In the present experiments, further products [(XIII) and (XIV)] were formed by elimination of the 5-hydroxy- or 5-acetoxy-group. Under acid conditions, the 5-acetoxyl was eliminated much more readily than the 5-hydroxyl group; elimination of both groups occurred rapidly with alkalis. The $\Delta^{8(9)}$-7 : 11-diols isolated in these experiments were recognised mainly by their active hydrogen content and by the absence of the absorption bands of conjugated systems. By analogy with similar compounds already described, they have been designated 7ξ : 11α-diols.

The products from experiments already mentioned include two unconjugated 7-ketones, which are probably the $C_{(8)}$-epimers (XI*A*) and (XI*B*); in the ergosterol D series, it appears that the monoepoxide can rearrange similarly to either of the $C_{(8)}$-epimeric 7-ketones (Budziarek, Stevenson, and Spring, *J.*, 1952, 4874). It is believed that the more lævorotatory isomers have the 8β(normal)-configuration (see also Budziarek and Spring, *J.*, 1953, 956). A pair of isomers in a related series described by Djerassi, Mancera, Stork, and Rosenkranz (*J. Amer. Chem. Soc.*, 1951, **73**, 4496) differ by 270° in molecular rotation, and may also be $C_{(8)}$-epimers. The structures (XI*A*) and (XI*B*), which have a 9 : 11-double bond, are consistent with the nature of the absorption near 200 mμ (Bladon, Henbest, and Wood, *loc. cit.*).

Compounds (XII) and (XIII) were characterised by the absorption bands of the αβ-unsaturated ketone systems. Alkali converted both compounds into (XIV), whose structure follows from these two modes of formation and from light-absorption data.

## Experimental

Optical rotations were determined on 0·5—2% solutions in chloroform at 15—25°. Infrared absorptions were measured for 5% solutions in chloroform with a sodium chloride prism and a Grubb–Parsons single-beam spectrophotometer. Ultra-violet absorption measurements were made with a Unicam SP. 500 instrument, "P.I. rectified spirit" being the solvent, and concentrations 1—3 × $10^{-4}$ mole/l. Hopkin and Williams's alumina was used for chromatographic separations; unless stated otherwise, the alumina was deactivated, by treatment with acetic acid as described by Farrar, Hamlet, Henbest, and Jones (*J.*, 1952, 2657). Light petroleum of b. p. 60—80° was used throughout. Specimens for analysis were dried at 70—80°/0·005 mm. for 12 hr. Chromatograms were eluted with solvents in the conventional order.

*Ergosteryl "α"-Acetate.*—This was prepared by the published procedure, and had m. p. 132—136°, $[\alpha]_D$ −87° (Heilbron and Sexton, *J.*, 1929, 921, give m. p. 132—133°). Repeated crystallisation from benzene–methanol gave ergosteryl acetate, m. p. 170—172°, $[\alpha]_D$ −86°. The "α"-acetate with digitonin solution gave ergosterol digitonide (40%). The supposed "α"-acetate is therefore a mixture or loose molecular compound of ergosterol and ergosteryl acetate.

*Ergosta-7 : 9 : 22-triene-3β : 5α-diol* (II; R = R′ = H).—In the preparation of the 3-monoacetate (m. p. 217—218°, $[\alpha]_D$ +50°, $\lambda_{max.}$ 243 mμ, ε 15,800) from ergosterol by the method of Jones *et al.* reproducible yields (75—80%) were obtained at the hydrogenation stage only when fresh ethyl acetate and fresh Raney nickel were employed. The diol (80%; m. p. 215—217°, $[\alpha]_D$ +44°) was prepared by alkaline hydrolysis of the acetate, or (42%) by Windaus, Bergmann, and Butte's method (*Annalen*, 1930, **477**, 268), and was converted by acetic anhydride–pyridine at 20° into the 3-acetate. Benzoyl chloride–pyridine at 20° gave the *3-benzoate*, m. p. 212—213°, $[\alpha]_D$ +47° (Found: C, 81·0; H, 8·9. $C_{35}H_{48}O_3$ requires C, 81·4; H, 9·4%). The 3-acetate (9·55 g.), diethylaniline (22 c.c.), and acetyl chloride (5 c.c.) in chloroform (5 c.c.) were refluxed for 4 hr., and yielded the 3 : 5-diacetate (90%), m. p. 139—140° (from methanol), $[\alpha]_D$ +95°, $\lambda_{max.}$ 242 mμ (ε 15,200), which was similarly obtained (80%) from the 3 : 5-diol [Jones *et al.*, give m. p. 142—143°, $[\alpha]_D$ +92°, $\lambda_{max.}$ 245 mμ (ε 15,000), for the diacetate]. The 3 : 5-diacetate (572 mg.), aqueous 1·2N-potassium hydroxide (5 c.c.) and methanol (75 c.c.) were refluxed for 90 min. Crystallisation from methanol afforded *5α-acetoxyergosta-7 : 9 : 22-trien-3β-ol* (90%) as needles, m. p. 162—163°, $[\alpha]_D$ +87°, $\lambda_{max.}$ 243 mμ (ε 15,100) (Found: C, 79·1; H, 10·4. $C_{30}H_{46}O_3$ requires C, 79·3; H, 10·1%). This contained one active hydrogen atom (Zerewitinoff) and formed a digitonide. Acetic anhydride–pyridine gave the 3 : 5-diacetate; prolonged hydrolysis of the latter gave the 3 : 5-diol (62%).

*5α-Acetoxyergosta-7 : 9 : 22-trien-3β-yl Toluene-p-sulphonate* (II; R = *p*-$C_6H_4$·$SO_2$, R′ = Ac).—The above 5α-acetoxy-sterol (593 mg.) (rigorously dried), pyridine (25 c.c.), and toluene-*p*-sulphonyl chloride (1075 mg.) were left for 16 hr. in the dark. Dioxan (5 c.c.), acetone (20 c.c.), and a little water were added; after 16 hr. at −5°, crystals of the *5α-acetate 3β-toluene-p-sulphonate* (72%), m. p. 130°, $[\alpha]_D$ +77°, $\lambda_{max.}$ 224 (ε 15,900), 242 (ε 14,200), and 325 mμ (ε 140) (Found: C, 73·1; H, 8·9. $C_{37}H_{52}O_5S$ requires C, 73·2; H, 8·6%), were obtained. The ester was somewhat unstable.

*3α-Acetoxyergosta-5 : 7 : 9 : 22-tetraene* (epi*Dehydroergosteryl Acetate*) (III).—The toluene-*p*-sulphonate (483 mg.) and pyridine (25 c.c.) were refluxed for 24 hr., the solution was poured into dilute hydrochloric acid, and the steroids were isolated with ether and dissolved in light petroleum–benzene (1 : 1) (40 c.c.). Chromatography on alumina (50 g., 2 × 20 cm.) and elution with light petroleum–benzene (4 : 1) gave *3α-acetoxyergosta-5 : 7 : 9 : 22-tetraene* (68%), needles (from methanol), m. p. 137—138°, $[\alpha]_D$ +200°, $\lambda_{max.}$ 324 mμ (ε 11,600) (Found: C, 82·4; H, 10·3. $C_{30}H_{44}O_2$ requires C, 82·6; H, 10·1%). The acetate (96 mg.), methanol (30 c.c.), and aqueous 10% potassium hydroxide (2 c.c.) when refluxed for 40 min. gave the *3α-hydroxy*-compound (epi*dehydroergosterol*), which from methanol formed needles, m. p. 144—145°, $[\alpha]_D$ +194°, $\lambda_{max.}$ 325 mμ (ε 11,600) (Found: C, 83·7; H, 10·8. $C_{28}H_{42}O,0{\cdot}5CH_3$·OH requires C, 83·4; H, 10·7%). The solvate contained 1·3 active hydrogen atoms (calc., 1·5), and gave no precipitate with digitonin in 95% ethanol. Lithium aluminium hydride tended to reduce the 5 : 6-double bond, and was unsuitable for conversion of the acetate into the sterol. The m. p. of the sterol was depressed considerably on admixture with its acetate or with dehydroergosterol.

*Rate of Formation of 3α-Acetoxyergosta-5 : 7 : 9 : 22-tetraene.*—In these experiments, no attempt was made to isolate products. At suitable intervals, small aliquots of the reaction media were withdrawn and the 5 : 7 : 9-triene absorption band at 325 mμ measured.

(a) *In ethanol.* The above toluene-*p*-sulphonate (23·4 mg.) and ethanol (25 c.c.) were refluxed :

| Time (hr.) ..... | 0 | 0·25 | 0·5 | 1 | 1·5 | 3·5 |
|---|---|---|---|---|---|---|
| ε at 242 mμ ..... | 14,000 | 12,400 | 12,000 | 11,800 | 11,700 | 9,600 |
| ε at 325 mμ ..... | 140 | 150 | 190 | 220 | 260 | 730 |

No reaction was observed in a similar experiment in which 10% aqueous potassium hydroxide (5 c.c.) was added.

(b) *In pyridine at* 25°. The sterol (10 mg.) was dissolved in pyridine (50 c.c.) kept at 25° :

| Time (days) ..... | 0 | 1 | 3 | 14 |
|---|---|---|---|---|
| ε at 325 mμ ..... | 120 | 180 | 300 | 550 |

(c) *In pyridine at* 115°. The steroid (36·2 mg.) was dissolved in pyridine (25 c.c.) and refluxed :

| Time (hr.) ... | 0 | 0·5 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 24 | 30 | 48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ε at 325 mμ | 200 | 1700 | 1930 | 2470 | 3050 | 3660 | 4180 | 4780 | 5470 | 6100 | 9000 | 9400 | 10,900 |

These results fit the following modified first-order kinetic equation $kt/a = \log_e [a/(a - x)] - x/a$ (where $k$ is a constant, $a$ is the initial concentration of steroid toluenesulphonate, and $x$ is the concentration of triene after $t$ min.).

(d) *In pyridine at* 115°, *with added toluene*-p-*sulphonic acid.* The steroid (23·1 mg.), anhydrous toluene-*p*-sulphonic acid (21·5 mg.), and pyridine (25 c.c.) were refluxed :

| Time (hr.) ..... | 1 | 2 | 3 | 4 | 6 | 8 | 24 | 29 | 48 | 55 | 72 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ε at 325 mμ ... | 805 | 1200 | 1560 | 2040 | 2930 | 3820 | 5750 | 5980 | 6800 | 6900 | 7600 |

(e) *In pyridine at* 115°, *with added sodium acetate.* The steroid (17·7 mg.), powdered fused sodium acetate (68·3 mg.), and pyridine (25 c.c.) were refluxed :

| Time (hr.) ..... | 1 | 2 | 5 | 11 | 24 | 48 |
|---|---|---|---|---|---|---|
| ε at 325 mμ ..... | 170 | 120 | 140 | 235 | 405 | 770 |

*5α-Acetoxy-9α : 11α-epoxyergosta-7 : 22-dien-3β-ol* (IV; R = H, R′ = Ac).—The 5-acetoxy-7 : 9 : 22-triene (485 mg.) was treated with 1·2 equivs. of monoperphthalic acid in ether (56 c.c.) (the per-acid solution was made by the procedure of Bohme, *Org. Synth.*, 1940, **20**, 70). After 20 hr. at 28°, the solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The resulting syrup, dissolved in benzene (30 c.c.), was chromatographed on alumina (50 g.; 2 × 20 cm.). A benzene–ether (1 : 1) eluate (490 mg.) was rechromatographed and crystallised from methanol, to afford the *epoxide* (40%), m. p. 163—164°, $[\alpha]_D$ +48°, $\lambda_{max.}$ 206 mμ (ε 6500) (Found : C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%).

*9α : 11α-Epoxyergosta-7 : 22-diene-3β : 5α-diol* (IV; R = R′ = H).—The triene diol (430 mg.) was treated with 1·2 mols. of perbenzoic acid in benzene (56 c.c.) (the per-acid solution was prepared by the method of Kolthoff *et al.*, *loc. cit.*). After 6 hr. at 28°, the steroids were isolated as in the previous example and chromatographed. Elution with ether–ethanol (9 : 1) gave the *epoxide* (79%), needles (from methanol), m. p. 214—217°, $[\alpha]_D$ −4°, $\lambda_{max.}$ 207 mμ (ε 6600) (Found : C, 78·5; H, 10·3. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). The epoxide and acetic anhydride–pyridine at 30° gave the 3-acetate (see below).

*Other Acetates of 9α : 11α-Epoxyergosta-7 : 22-diene-3β : 5α-diol.*—The epoxide 3 : 5-diacetate (70%), m. p. 128°, $[\alpha]_D$ +50°, $\lambda_{max.}$ 205 mμ (ε 6800), was obtained by using perbenzoic acid in benzene (Jones *et al.* give m. p. 125—127°, $[\alpha]_D$ +51·5°). Hydrolysis with potassium hydroxide in aqueous methanol gave a difficultly separable mixture of the diol and the 5-acetate (see above). The epoxide 3-acetate (60%, together with 35% of unchanged material), m. p. 237—238°, $[\alpha]_D$ +4°, $\lambda_{max.}$ 206 mμ (ε 7100), was obtained from the 3-acetoxy-5-hydroxy-triene and monoperphthalic acid in ether (Jones *et al.* give m p. 229—237°, $[\alpha]_D$ +2°). In another experiment, the 3-acetoxy-5-hydroxy-triene (5·3 g.) in benzene (50 c.c.) was treated with 1·3 mols. of monoperphthalic acid in ether (72 c.c.) at 20° for 48 hr. The solution was washed with aqueous sodium hydrogen carbonate, and the product recrystallised from methanol–benzene, giving the epoxide 3-acetate (3 g.), m. p. 234—236°. The mother-liquors were evaporated and the residue chromatographed in benzene (50 c.c.) on alumina (50 g.; 2 × 20 cm.). The benzene eluate (700 mg.; m. p. 206—208°) was again chromatographed; elution with benzene–ether (9 : 1) gave successively *3β-acetoxy-7ξ : 8ξ-9α : 11α-diepoxyergost-22-en-5α-ol* (V;

R = Ac, R′ = H) (3%), platelets (from methanol–benzene), m. p. 234—235°, $[\alpha]_D$ −10°, $\lambda_{max.}$ 203 mμ (ε 1020) (Found: C, 74·25; H, 10·0. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%), and 3β-*acetoxy*-5α-*hydroxy*-8β-*ergosta*-9 : 22-*dien*-7-*one* (XI*B*; R = Ac, R′ = H) (3%), m. p. 206—208°, $[\alpha]_D$ −40°, $\lambda_{max.}$ 206 mμ (ε 3050) (Found: C, 76·25; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%). The 7-ketone gave a yellow 2 : 4-dinitrophenylhydrazone. The diepoxide with potassium hydroxide in aqueous methanol or with lithium aluminium hydride in ether–dioxan gave the 3β : 5α-*dihydroxydiepoxide* (V; R = R′ = H) (95%) which crystallised from methanol–benzene as plates, m. p. 251—252°, $[\alpha]_D$ −18°, $\lambda_{max.}$ 206 mμ (ε 1200) (Found: C, 74·15; H, 9·9. $C_{28}H_{44}O_4,0{\cdot}5CH_3{\cdot}OH$ requires C, 74·3; H, 10·0%), and was reconverted by acetic anhydride–pyridine into the 3-acetate. From another experiment with the 3-acetoxy-5-hydroxy-triene (4 g.) and 1·3 mols. of monoperphthalic acid in chloroform–ether (1 : 1; 135 c.c.) at 0° for 24 hr., then at 25° for 24 hr., and chromatography on alumina (300 g.; 5 × 60 cm.), the following were the main products: unchanged triene (15%); 3β-*acetoxy*-5α-*hydroxy*-8α-*ergosta*-9 : 22-*dien*-7-*one* (XI*A*; R = Ac, R′ = H) (8%), needles (from methanol), m. p. 143—144°, $[\alpha]_D$ +17°, $\lambda_{max.}$ 205 mμ (ε 3500) (Found: C, 76·95; H, 9·5. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%) (slowly formed a 2 : 4-dinitrophenylhydrazone), 3β-acetoxy-7ξ : 8ξ-9α : 11α-diepoxyergost-22-en-5α-ol (15%), m. p. 226—228°, $[\alpha]_D$ −7°, $\lambda_{max.}$ 204 mμ (ε 900), and 3β-*acetoxy*-5α-*hydroxyergosta*-8(9) : 22-*dien*-7-*one* (XII; R = Ac, R′ = H), m. p. 237—238°, $[\alpha]_D$ −83°, $\lambda_{max.}$ 256 mμ (ε 9300) (Found: C, 76·3; H, 9·6. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%) (slowly formed a crimson 2 : 4-dinitrophenylhydrazone).

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (VI; R = Ac).—The 3β-acetoxy-5α-hydroxy-epoxide was treated with boron trifluoride–ether complex in benzene as described by Jones *et al.* but for 72 hr. The product was chromatographed on alumina; elution with light petroleum–benzene (1 : 1; 50 c.c.) gave 3β-*acetoxyergosta*-5 : 8(9) : 22-*trien*-11-*one* (VII) (13%), needles (from methanol), m. p. 128°, $[\alpha]_D$ −34°, $\lambda_{max.}$ 249 mμ (ε 10,800) (Found: C, 79·9; H, 9·9. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%); this was hydrolysed by alkali to the *sterol*, m. p. 125—126°, $[\alpha]_D$ −33°, $\lambda_{max.}$ 249 mμ (ε 11,600) (Found: C, 82·2; H, 11·5. $C_{28}H_{42}O_2$ requires C, 81·95; H, 10·25%). Further elution, finally with benzene, gave 3β-acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (53%), m. p. 189°, $[\alpha]_D$ −122°, $\lambda_{max.}$ 207 (ε 4000) and 292 mμ (ε 180) which appeared to react slowly with 2 : 4-dinitrophenylhydrazine {Jones *et al.*, give m. p. 181—187°, $[\alpha]_D$ −135°, $\lambda_{max.}$ 293 mμ (ε 190)}. Further elution with benzene–ether (9 : 1) gave 15% of mixed dien-11-ones. Reduction of the time of the reaction to 7 hr. improved the yield of 7 : 22-dien-11-one to 75%; in this case, the crude product was crystallised from methanol–benzene, without chromatography.

*Base-catalysed Rearrangement of* 3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one*.—(*a*) The ketone was unaltered by filtration of a benzene solution through a column of untreated alumina.

(*b*) The ketone (620 mg.), 10% aqueous potassium hydroxide (5 c.c.), and methanol (70 c.c.) were refluxed for 2½ hr. The steroids were dissolved in benzene (50 c.c.) and chromatographed on alumina (50 g.; 2 × 20 cm.). Elution with benzene–ether (1 : 1) and crystallisation from methanol afforded a *compound* (58%), as needles, m. p. 184—186°, $[\alpha]_D$ +19°, $\lambda_{max.}$ 243 mμ (ε 7500) (Found: C, 78·5; H, 10·7. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). Further elution with ether–ethanol (9 : 1) gave 3β : 5α-*dihydroxyergosta*-8(9) : 22-*dien*-11-*one* (IX; R = R′ = H) as needles, m. p. 223—224°, $[\alpha]_D$ +75°, $\lambda_{max.}$ 256 mμ (ε 6400) (Found: C, 78·2; H, 10·25. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%).

(*c*) The ketone (158 mg.), Amberlite resin " IRA 400-OH " (0·5 g.), and methanol (40 c.c.) were refluxed for 16 hr. The steroid product was boiled for 30 min. with acetic anhydride (5 c.c.), and the acetic anhydride removed. The residue was chromatographed in light petroleum–benzene (1 : 1; 40 c.c.) on alumina (15 g.; 1 × 15 cm.); elution with light petroleum–benzene (1 : 1) and crystallisation from methanol gave a *compound* (37%), m. p. 177—179°, $[\alpha]_D$ +33°, $\lambda_{max.}$ 243 mμ (ε 10,950) (Found: C, 75·4; H, 10·15. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%). After the benzene eluates which followed had been discarded, elution with benzene–ether (9 : 1) and then crystallisation from methanol afforded 3β-*acetoxy*-5α-*hydroxy*-*ergosta*-8(9) : 22-*dien*-11-*one* (IX; R = Ac, R′ = H) (26%), m. p. 191—193°, $[\alpha]_D$ +74°, $\lambda_{max.}$ 256 mμ (ε 8400) (Found: C, 77·0; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%); which does not form a 2 : 4-dinitrophenylhydrazone [Jones *et al.* give m. p. 192—197°, $[\alpha]_D$ +81°, $\lambda_{max.}$ 257 mμ (ε 9100)]. The same acetate was obtained from the corresponding 3 : 5-diol (above) and acetic anhydride–pyridine at 25°.

*Acid-catalysed Rearrangement of* 3β-*Acetoxy*-5α-*hydroxy*-9β-7 : 22-*dien*-11-*one*.—The ketone (673 mg.), N-sulphuric acid (30 c.c.), and dioxan (50 c.c.) were refluxed for 90 min. The crude steroid product was refluxed for 30 min. with acetic anhydride (30 c.c.), then chromatographed in

light petroleum–benzene (1 : 1; 30 c.c.) on alumina (50 g., 2 × 20 cm.). Later fractions eluted by light petroleum–benzene were crystallised from methanol, to give 3β : 5α-diacetoxyergosta-8(9) : 22-dien-11-one (3%), m. p. 150—152°, $[\alpha]_D$ +93°, $\lambda_{max.}$ 254 mμ (ε 6500) (Found : C, 74·5; H, 9·45. Calc. for $C_{32}H_{48}O_5$ : C, 75·0; H, 9·4%) [Jones *et al.* give m. p. 150—153°, $[\alpha]_D$ +121°, $\lambda_{max.}$ 254 mμ (ε 9000)]. From further light petroleum–benzene (1 : 1) eluates, a steroid *acetate* (13%), m. p. 199—202°, $[\alpha]_D$ −25°, $\lambda_{max.}$ 243 mμ (ε 11,000) (Found : C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%), was obtained; the same acetate was made from the compound $C_{28}H_{44}O_3$, m. p. 184—186° (above), and acetic anhydride–pyridine at 25°, or acetic anhydride at 115°. Continued elution, with benzene–ether (9 : 1), gave 3β-acetoxy-5α-hydroxyergosta-8(9) : 22-dien-11-one (43%), m. p. 196—197°, $[\alpha]_D$ +66°, $\lambda_{max.}$ 256 mμ (ε 6600).

3β-*Acetoxy-5α-hydroxyergost-22-en-11-one* (VIII).—3β-Acetoxy-5α-hydroxyergosta-8(9) : 22-dien-11-one (95 mg.) in dry ether (12 c.c.) was added to anhydrous liquid ammonia (150 c.c.). Lithium (25 mg.) was added and the solution stirred for 30 min. A trace of ferric nitrate was added to the (blue) solution to destroy the remaining lithium, and the ammonia was removed in a vacuum. The steroids were isolated and left at 25° for 16 hr. with acetic anhydride (1 c.c.) and pyridine (10 c.c.). The product was chromatographed in light petroleum–benzene (1 : 1; 20 c.c.) on alumina (10 g., 1 × 10 cm.). Benzene eluates were crystallised from aqueous methanol, to afford the *22-en-11-one* (55%) as needles, m. p. 221—222°, $[\alpha]_D$ 0, $\lambda_{max.}$ 205 mμ (ε 2500) (Found : C, 73·85; H, 9·7. $C_{30}H_{48}O_4,CH_3{\cdot}OH$ requires C, 73·8; H, 10·3%) [Jones *et al.* (personal communication) have made this compound independently and find m. p. 210—220°, $[\alpha]_D$ 0].

*Acid Treatment of* 3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene*.—(*a*) The epoxide (620 mg.), 2N-sulphuric acid (20 c.c.), and dioxan (100 c.c.) were shaken at 25° for 30 min. The steroid product was chromatographed in light petroleum–benzene (1 : 1, 20 c.c.) on alumina (50 g.; 2 × 20 cm.). Elution with benzene–ether (1 : 1) and crystallisation from methanol gave needles of 3β : 5α-*diacetoxy*-7ξ : 11α-*dihydroxyergosta*-8(9) : 22-*diene* (X; R = R′ = Ac) (12%), m. p. 152—153°, $[\alpha]_D$ +41°, $\lambda_{max.}$ 207 mμ (ε 7000) (Found : C, 72·4; H, 9·3. $C_{32}H_{50}O_6$ requires C, 72·5; H, 9·4%); unchanged epoxide (67%) was also obtained.

(*b*) The epoxide (504 mg.), 5N-sulphuric acid (15 c.c.), and dioxan (100 c.c.) were shaken at 25° for 4 hr., and the product was chromatographed. The light petroleum–benzene (1 : 1) elutates (350 mg.) were crystallised from methanol, to give 3β-*acetoxyergosta*-5 : 9 : 22-*trien*-7-*one* (XIII; R = Ac) (20%), m. p. 171—172°, $[\alpha]_D$ −112°, $\lambda_{max.}$ 235 mμ (ε 13,300) (Found : C, 79·9; H, 9·6. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%). Infra-red bands : 7126 cm.$^{-1}$ (acetoxy-group); doublet at 1668 and 1600 cm.$^{-1}$ (αβ-unsaturated ketone system). The Tortelli–Jaffé test was positive and the compound slowly formed a crimson 2 : 4-dinitrophenylhydrazone. The 7-ketone (110 mg.), refluxed for 1 hr. with N-potassium hydroxide (5 c.c.) in methanol (30 c.c.), afforded the 3β-*hydroxy*-5 : 8(9) : 22-*trien*-7-*one* (XIV; R = H), m. p. 166—168°, $[\alpha]_D$ −12°, $\lambda_{max.}$ 246 mμ (ε 11,000) (Found : C, 81·7; H, 10·5. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·2%). This with cold acetic anhydride–pyridine (48 hr.) gave the 3-*acetate*, m. p. 193—194°, $[\alpha]_D$ −21°, $\lambda_{max}$ 245 mμ (ε 11,300) (Found : C, 79·2; H, 10·0. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%), which slowly formed a crimson 2 : 4-dinitrophenylhydrazone.

*Acid Treatment of* 3β-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*dien*-5α-*ol*.—(*a*) The epoxide (407 mg.), 4N-sulphuric acid (28 c.c.), and dioxan (100 c.c.) were shaken together for 30 min. The isolated steroids were dissolved in benzene (30 c.c.) and chromatographed on alumina (50 g.; 2 × 20 cm.). A solid (355 mg.) from benzene–ether eluates was not resolved. Further elution with ether–ethanol (9 : 1), and crystallisation from methanol, afforded *ergosta*-8(9) : 22-*diene*-3β : 5α : 7ξ : 11α-*tetrol* (X; R = R′ = H) (7%), m. p. 188—189°, $[\alpha]_D$ −15°, $\lambda_{max.}$ 208 mμ (ε 4900) (Found : C, 75·05; H, 9·95. $C_{28}H_{46}O_5$ requires C, 75·35; H, 10·3%).

(*b*) The epoxide (600 mg.), 4N-sulphuric acid (28 c.c.), and dioxan (100 c.c.) were left at 25° for 3 days. The crude steroid product was chromatographed; elution with benzene–ether (1 : 1; 600 c.c.) and crystallisation from methanol yielded 3β-hydroxyergosta-5 : 8(9) : 22-trien-7-one (XIV; R = H) (38%), m. p. and mixed m. p. 166—170°, $[\alpha]_D$ −17°, $\lambda_{max.}$ 245 mμ (ε 12,050). Continued elution with benzene–ether (1 : 1; 500 c.c.) gave 3β : 5α-*dihydroxy-ergosta*-9 : 22-*dien*-7-*one* (XI*B*; R = R′ = H) (20%), needles, m. p. 212—214°, $[\alpha]_D$ −61°, $\lambda_{max.}$ 204 (ε 3900) and 320 mμ (ε 93) (Found : C, 78·7; H, 10. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). Further elution with ether–ethanol (9 : 1) gave 3β : 5α-*dihydroxyergosta*-8(9) : 22-*diene*-7-*one* (XII; R = R′ = H) (43%), m. p. 240—242°, $[\alpha]_D$ −68°, $\lambda_{max}$ 257 (ε 7000) and 315 mμ (ε 225) (Found : C, 78·5; H, 10·0. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%), converted by acetic anhydride–pyridine at 25° into the 3-acetate, m. p. 225—228°, $[\alpha]_D$ −81°, $\lambda_{max}$ 257 mμ

(ε 9200). In an experiment similar to (*b*), the dihydroxy-epoxide (IV; R = R′ = H) gave the same three products in 29, 24, and 28% yield respectively.

(*c*) In one experiment, the epoxide (372 mg.) was dissolved in hot methanol–chloroform. As no crystals separated on cooling, the solution was evaporated and chromatographed, affording unchanged epoxide (35%) and 3β-acetoxy-5α-hydroxy-8α-ergosta-9 : 22-dien-7-one (XI*A*; R = Ac, R′ = H) (35%), m. p. and mixed m. p. 138—139°, $[\alpha]_D$ +14° (no significant ultraviolet absorption).

*Acid Treatment of* 3β-*Acetoxy*-5α-*hydroxyergosta*-9 : 22-*dien*-7-*one*.—The ketone (XI*B*; R = Ac, R′ = H) (195 mg.) was refluxed in dioxan (20 c.c.) and N-sulphuric acid (10 c.c.) for 90 min. The steroid product was treated with acetic anhydride (0·5 c.c.) and pyridine (10 c.c.) at 25° for 16 hr., then chromatographed in light petroleum–benzene (1 : 1; 30 c.c.) on alumina (50 g.; 2 × 20 cm.). Benzene eluates were crystallised from methanol, giving 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one (33%), m. p. 186—187°, $[\alpha]_D$ −9°, $\lambda_{max.}$ 244 mμ (ε 10,600). Finally, benzene–ether (1 : 1) eluted 3β-acetoxy-5α-hydroxyergosta-8(9) : 22-dien-7-one (36%), m. p. 234—235°, $[\alpha]_D$ −93°, $\lambda_{max.}$ 256 mμ (ε 8900).

*Alkali Treatment of* 3β-*Acetoxy*-5α-*hydroxyergostadien*-7-*ones*.—(*a*) The ketone (XII; R = Ac, R′ = H) (40 mg.), methanol (30 c.c.), and aqueous 10% potassium hydroxide (5 c.c.) were refluxed for 1 hr. Crystallisation from methanol afforded 3β-hydroxyergosta-5 : 8(9) : 22-trien-7-one (XIV; R = H), m. p. 160—166°, $[\alpha]_D$ −13°, $\lambda_{max.}$ 247 mμ (ε 10,000).

(*b*) The same product (92%), m. p. 163—164°, $[\alpha]_D$ −13°, $\lambda_{max.}$ 246 mμ (ε 10,200), was obtained similarly from 3β-acetoxy-5α-hydroxyergosta-9 : 22-dien-7-one (XI*B*; R = Ac, R′ = H), and from the 3β : 5α-dihydroxy-9 : 22-dien-7-one.

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## 643. *Isomerisation of Ethyl* α-2 : 3 : 4 : 5-*Tetrahydrobenzoylacetoacetate.*

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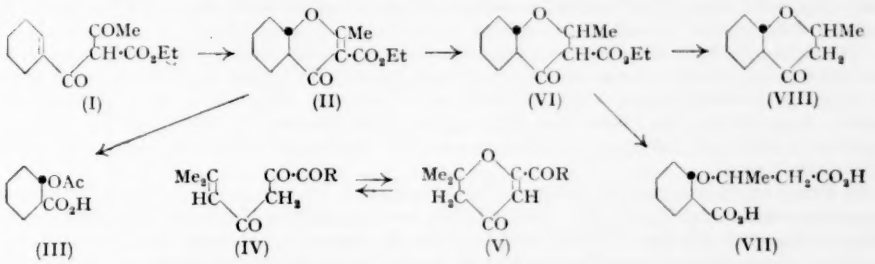
Ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (I) undergoes isomerisation to give ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (II). The latter affords *trans*-2-acetoxy*cyclo*hexane-1-carboxylic acid on ozonolysis, thus providing proof of both its structure and configuration.

IN connection with other work we have had occasion to condense 2 : 3 : 4 : 5-tetrahydrobenzoyl chloride with ethyl acetoacetate with the intention of obtaining ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (I) as an intermediate. When condensation was carried out in benzene using either ethyl sodioacetoacetate or ethyl ethoxymagnesioacetoacetate the product partly crystallised. The non-crystalline portion proved to be (I) as it gave a colour with ferric chloride as well as satisfactory analytical data, and also underwent methanolysis to methyl 2 : 3 : 4 : 5-tetrahydrobenzoylacetate. The crystalline material was shown by analysis to be isomeric and, as it gave no colour with ferric chloride, was believed to be ethyl 5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (II); this formulation was shown to be correct since ozonolysis afforded oxalic acid and 2-acetoxy-*cyclo*hexanecarboxylic acid. As the latter acid proved to be the *trans*-form (III), (II) must also have the *trans*-configuration.

The cyclisation of (I) to (II) is formally analogous with the well-established isomerisation of " mesityl oxide oxalic esters " (IV; R = OAlkyl) (Claisen, *Ber.*, 1891, **24**, 115; *Annalen*, 1896, **291**, 132; Dieckmann, *Ber.*, 1920, **53**, 1772; von Auwers and Dieckmann, *Ber.*, 1923, **56**, 1527) to derivatives of 5 : 6-dihydro-6 : 6-dimethyl-4-pyrone-2-carboxylic acid (V; R = OAlkyl), which is not, however, apparently shown by the related diethylamide (IV;

R = $NEt_2$) (Utzinger and Hoelle, *Helv. Chim. Acta*, 1952, **35**, 2054). It has also been shown that (IV; R = OAlkyl) and (V; R = OAlkyl) exist in equilibrium greatly favouring (V; R = OAlkyl) (Knorr and Schubert, *Ber.*, 1911, **44**, 2776) and catalysed in the forward direction by both acids and bases (Bell and Rybicka, *J.*, 1947, 24); excess of alkali alkoxide, however, gives the enol derivative of (IV; R = OBu) from (V; R = OBu) (Puetzer, Nield, and Barry, *J. Amer. Chem. Soc.*, 1945, **67**, 832). Although we have no precise evidence on this point it may well be that (I) and (II) also exist in equilibrium under suitable conditions; conversion of (I) into (II) appeared to be catalysed by hot ethanolic 0·01N-hydrochloric acid, and both acid and alkaline hydrolyses of (II) afforded acetyl*cyclo*hexene.




Catalytic hydrogenation of (II) gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchroman-4-one-3-carboxylate (VI), which appeared from its infra-red absorption spectrum and from the slowness with which it developed a colour with ferric chloride to exist entirely in the ketonic form; this contrasts with, for example, ethyl 2-oxo-*cyclo*hexane-1-carboxylate which is extensively enolised (Dieckmann, *Ber.*, 1922, **55**, 2470) and gives evidence, corroborated by us, of a chelated conjugated carbonyl group in its infra-red spectrum (Leonard, Gutowsky, Middleton, and Petersen, *J. Amer. Chem. Soc.*, 1952, **74**, 4070). The keto-ester (VI) readily underwent "acid" rather than "ketonic" hydrolysis, to give *trans*-β-2-carboxy*cyclo*hexyloxybutyric acid (VII), although hydrolysis in the cold with dilute aqueous alkali gave some of the free β-keto-acid passing with loss of carbon dioxide at the melting point into *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchroman-4-one (VIII).

## Experimental

2 : 3 : 4 : 5-*Tetrahydrobenzonitrile*.—Phosphoryl chloride (338 c.c.) was added to a stirred solution of *cyclo*hexanone cyanohydrin (300 g.) in technical pyridine (1700 c.c.) at such a rate that the heat of reaction brought the mixture to the b. p. When the addition was complete, the mixture was refluxed for a further ½ hr., then cooled somewhat, and poured on ice. After extraction with benzene, the organic phase was washed twice with water and fractionated, affording 2 : 3 : 4 : 5-tetrahydrobenzonitrile (238 g., 94%), b. p. 85—90°/17 mm., $n_D^{19}$ 1·4864. Ruzicka and Brugger (*Helv. Chim. Acta*, 1926, **9**, 399) record b. p. 81°/12 mm.

2 : 3 : 4 : 5-*Tetrahydrobenzoic Acid*.—The acid was prepared by alkaline hydrolysis of the nitrile (Boorman and Linstead, *J.*, 1935, 258, modified by Gardner and Rydon, *J.*, 1938, 48), followed by extraction with ether and distillation; it had b. p. 138—141°/18 mm., $n_D^{21}$ 1·5010. The distillate largely solidified and the solid was freed as far as possible from adhering oil on a sintered-glass funnel. The resulting solid (crude $\Delta^1$-isomer) was used for the preparation of the acid chloride.

2 : 3 : 4 : 5-*Tetrahydrobenzoyl Chloride*.—The tetrahydrobenzoic acid (100 g.) and thionyl chloride (66 c.c.) were mixed (endothermic reaction) and the mixture was warmed gently to keep the temperature at ≯30°. When the reaction had ceased, the mixture was rapidly fractionated (free flame); 2 : 3 : 4 : 5-tetrahydrobenzoyl chloride (112 g., 98%) passed over at 92—100°/18 mm. and had $n_D^{24}$ 1·5100.

*Ethyl* α-2 : 3 : 4 : 5-*Tetrahydrobenzoylacetoacetate* (I) *and Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-2-*methylchromone*-3-*carboxylate* (II).—(*a*) Ethyl acetoacetate (19·5 g.) in dry benzene (100 c.c.) was added to alcohol-free sodium ethoxide (from 4·6 g. of sodium) and, after formation of the sodio-derivative, the last of the ethanol was removed by co-distillation with part of the benzene. Tetrahydrobenzoyl chloride (11 g.) in dry benzene (50 c.c.) was added and the mixture

was refluxed for 1·5 hr. After being shaken with 2N-hydrochloric acid (100 c.c.), the organic phase was separated and washed with water, with aqueous sodium carbonate, and again with water. Fractionation then afforded a yellow viscous oil, b. p. 124—234°/0·7 mm., which partly crystallised during several hours. The crystalline material (5·8 g.) was isolated by stirring and washing with light petroleum, and recrystallisation from the same solvent gave pure *ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro*-2-*methylchromone*-3-*carboxylate* (II), which separated in colourless prisms, m. p. 66—67°; light absorption in EtOH: $\lambda_{max.}$ 255 mμ, log ε 4·01; $\lambda_{min.}$ 231 mμ, log ε 3·30; absorption bands (Nujol mull) in 1500—2000-cm.$^{-1}$ region at 1583, 1660, and 1720 cm.$^{-1}$ (in order of increasing strength) (Found: C, 65·4; H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The substance gave no colour with ferric chloride but it gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethanol–ethyl acetate in felted orange needles, m. p. 163° (Found: C, 54·5; H, 5·2; N, 13·1. $C_{19}H_{22}O_7N_4$ requires C, 54·5; H, 5·3; N, 13·4%).

The light petroleum filtrates, after removal of the above crystalline solid, were evaporated, and the residual oil (8·5 g.) was distilled, yielding *ethyl* α-2 : 3 : 4 : 5-*tetrahydrobenzoylacetoacetate* (I) as a nearly colourless oil, b. p. 120—125° (bath)/0·3 mm., $n_D^{18}$ 1·5132; light absorption in EtOH: $\lambda_{max.}$ 244 mμ, log ε 3·95; $\lambda_{infl.}$ 264 mμ, log ε 3·80 (Found: C, 65·3; H, 7·8. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The substance gave a cherry-red colour with ferric chloride in alcoholic solution.

(*b*) Ethyl ethoxymagnesioacetoacetate * was prepared by the technique used for ethoxymagnesiomalonic ester (Lund, *Ber.*, 1934, **67**, 935) from magnesium (3·6 g.), ethanol (10 c.c.), and ethyl acetoacetate (19·5 g.) in benzene (40 c.c.) in the presence of carbon tetrachloride (1 c.c.), excess of ethanol being eventually removed by co-distillation with added benzene. Tetrahydrobenzoyl chloride (14·4 g.), dissolved in benzene, was then added slowly at 0° and reaction was completed under reflux for 1 hr. Subsequent treatment of the mixture in the manner outlined above gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (7·4 g.) and ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (13 g.).

*Isomerisation of Ethyl* α-2 : 3 : 4 : 5-*Tetrahydrobenzoylacetoacetate* (I) *to Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-2-*methylchromone*-3-*carboxylate* (II).—A sample of ethyl tetrahydrobenzoylacetoacetate was kept until no further separation of crystalline material took place and a portion (5 g.) of the decanted oil was refluxed for 4 hr. with ethanolic 0·01N-hydrochloric acid (50 c.c.). Removal of the solvent under reduced pressure gave a residue which partly crystallised; treatment with light petroleum as described above gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (2·35 g.), m. p. 65°, not depressed on admixture with the specimens previously obtained.

*Methyl* 2 : 3 : 4 : 5-*Tetrahydrobenzoylacetate*.—Ethyl tetrahydrobenzoylacetoacetate (32 g.) was added to a methanolic solution (100 c.c.) of sodium methoxide (from 3·2 g. of sodium), and the mixture was set aside at room temperature for 16 hr. The solution was acidified by being run into water simultaneously with dilute hydrochloric acid, the pH being kept at ~3·5—4·0. The product was isolated by means of ether, and fractionation gave, after a small fore-running, *methyl* 2 : 3 : 4 : 5-*tetrahydrobenzoylacetate* (14·5 g., 55%), b. p. 95°/0·4 mm., $n_D^{22}$ 1·5009 (Found: C, 65·9; H, 7·9. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The substance gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate–methanol in orange leaflets, m. p. 125—126° (Found: C, 52·9; H, 4·8; N, 15·1. $C_{16}H_{18}O_6N_4$ requires C, 53·0; H, 5·0; N, 15·5%), and a *phenylpyrazolone*, which crystallised from aqueous methanol in yellow needles, m. p. 120—122° (Found: C, 74·7; H, 6·7; N, 12·0. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·6%).

*Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-2-*methylchroman*-4-*one*-3-*carboxylate* (VI).—Ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (3 g.) was hydrogenated in methanol (100 c.c.) at room temperature and atmospheric pressure in presence of palladised strontium carbonate (1 g.), one mol. of hydrogen being slowly absorbed (18 hr.). Evaporation of the filtered solution gave an oily residue which, crystallised from light petroleum, afforded pure *ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro*-2-*methylchroman*-4-*one*-3-*carboxylate* as rosettes of fine colourless needles (2·05 g.), m. p. 67—68·5°, b. p. 85—90° (bath)/0·005 mm.; light absorption in EtOH: $\lambda_{max.}$ 262 mμ, log ε 1·71; $\lambda_{min.}$ 245 mμ, log ε 1·60; strong absorption bands (Nujol mull) in the 1500—2000-cm.$^{-1}$ region at 1700 and 1712 cm.$^{-1}$ (Found: C, 65·1; H, 8·1. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%). The substance gave no immediate colour with ferric chloride in alcoholic solution but a clear purple colour developed slowly. It gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethanol–ethyl acetate in orange prisms, m. p. 213—215° (Found: N, 13·0. $C_{19}H_{24}O_7N_4$ requires N, 13·3%).

* Since this reaction was carried out the method has been described as a general one for the synthesis of acylacetoacetic esters by Viscontini and Merckling (*Helv. Chim. Acta*, 1952, **35**, 2280).

*Hydrolysis of Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchromone-3-carboxylate* (II).—(a) *Alkaline hydrolysis.* A solution of ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (5 g.) in methanolic 5% potassium hydroxide (100 c.c.) was refluxed for 1 hr. After cooling and dilution with water, extraction with ether gave an oil (1·74 g.), $n_D^{16}$ 1·4961, shown to be acetyl*cyclo*hexene by the formation of a 2 : 4-dinitrophenylhydrazone, red needles, m. p. 194—196° not depressed on admixture with an authentic specimen.

(b) *Acid hydrolysis.* The compound (II) (1 g.) dissolved readily on warming with concentrated hydrochloric acid (5 c.c.) and was then kept at room temperature overnight. Dilution with water and extraction with ether gave an oil (0·39 g.) shown, as above, to be acetyl*cyclo*hexene.

*Ozonolysis of Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchromone-3-carboxylate* (II).—The compound (II) (0·5 g.), in carbon tetrachloride (25 c.c.), was treated at 0° with a stream of ozonised oxygen for 1 hr. After removal of the solvent under reduced pressure the resultant gummy ozonide was warmed on the steam-bath with hydrogen peroxide (25 c.c. of 20-vol. solution) for ½ hr. The mixture was cooled and extracted with ether. The aqueous phase was treated with a small volume of aqueous calcium chloride; the precipitated calcium salt was collected and dissolved in a little dilute hydrochloric acid, and the solution (diluted to 5 c.c. with water) gave a positive test for oxalic acid with resorcinol and concentrated sulphuric acid (Meyer, " Nachweis und Bestimmung organischer Verbindungen," p. 131, Springer, Berlin, 1933). The ethereal solution was extracted with sodium hydrogen carbonate solution, and the acid fraction was recovered by acidification and extraction with ether. The resulting oil (190 mg.) partly solidified and gave, after two recrystallisations from ether–light petroleum, *trans*-2-acetoxy*cyclo*hexane-1-carboxylic acid (III), m. p. 101—102°, not depressed on admixture with an authentic specimen of m. p. 102—103° prepared by the method of Pascual, Sistaré, and Regás (*J.*, 1949, 1943), who record m. p. 104·5—105·5° (corr.).

*Hydrolysis of Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchroman-4-one-3-carboxylate* (VI).—(a) *Mild alkaline hydrolysis.* A suspension of (VI) (5 g.) in aqueous 0·5N-sodium hydroxide (100 c.c.) was shaken at room temperature overnight. The resultant clear solution was acidified (Congo-red) with dilute sulphuric acid and kept at 0° for 24 hr.; trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro-2-methylchroman-4-one-3-carboxylic acid* (2·19 g.), m. p. 139° (decomp.) then separated in rosettes of needles. Recrystallisation from chloroform–light petroleum, attended by considerable loss, raised the m. p. to 140—141° (Found : C, 61·7; H, 7·4. $C_{11}H_{16}O_4$ requires C, 62·2; H, 7·5%). The β-keto-acid gave a violet colour with ferric chloride in aqueous solution and a purple colour in methanolic solution. On heating for a minute above the m. p., it afforded trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro-2-methylchroman-4-one* (VIII) as a colourless oil, b. p. 115° (bath-temp.)/18 mm., $n_D^{20}$ 1·4862 (Found : C, 71·2; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), giving a 2 : 4-*dinitrophenylhydrazone*, crystallising from methanol–ethyl acetate in yellow needles, m. p. 218° (Found : C, 55·5; H, 5·9; N, 16·0 $C_{16}H_{20}O_5N_4$ requires C, 55·1; H, 5·8; N, 16·1%).

The aqueous solution after separation of the above β-keto-acid was saturated with sodium chloride and extracted twice with ether. The combined extracts, dried and evaporated, yielded a viscous oil (2·6 g.) which slowly solidified. Crystallisation from benzene–light petroleum gave hard prisms of trans-β-2-*carboxy*cyclo*hexyloxybutyric acid* (VII) (1·6 g.), m. p. 129—130° (Found : C, 57·2; H, 8·1. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·9%).

(b) *Concentrated alkaline hydrolysis.* The compound (VI) (3 g.) was refluxed with methanolic 20% potassium hydroxide solution (50 c.c.) for 45 min., and the mixture, after cooling, was poured into an excess of dilute sulphuric acid. A precipitate appeared but quickly redissolved. After saturation with sodium chloride and extraction with ether, an acid fraction (2·4 g.) was recovered by extraction with sodium hydrogen carbonate, acidification, and re-extraction with ether. The acid slowly solidified and crystallisation from ethyl acetate–light petroleum gave *trans*-β-2-carboxy*cyclo*hexyloxybutyric acid (VII) (2·12 g., 74%), identical with that obtained above.

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## 644. *Perhydroindanes. Part II.* Hexahydroindanones.*

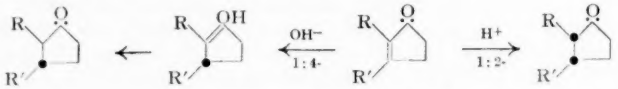
By DAVID W. MATHIESON.

Reduction at a palladium catalyst of a number of 4 : 5 : 6 : 7-tetrahydroindanones has been shown to lead to the corresponding hexahydroindanones in good yield.

PREVIOUSLY recorded routes to hexahydroindanone and its derivatives have suffered from the inaccessible nature of the intermediate materials. For instance, synthesis of hexahydroindan-1-one involves Dieckmann ring closure of the diester of β-(2-carboxy*cyclo*hexyl)-propionic acid (cf., *inter al.*, Hückel, Sachs, Yantschulewitsch, and Nerdel, *Annalen*, 1935, **518**, 155; Kon, Linstead, and Simmons, *J.*, 1937, 814). Alternatively, the 8-methyl derivative may be made by a Darzens reaction on β-(2-methyl*cyclo*hex-1-enyl)propionic acid followed by reduction of the double bond (Chuang, Tien, and Ma, *Ber.*, 1936, **69**, 1494; Nenitzescu and Przemetsky, *Ber.*, 1941, **74**, 676, 6841). Obvious difficulties of synthesis arise, however, when hexahydroindanones more complex than the parent members of the series are required. The elegant work of Johnson and his co-workers on the Stobbe condensation (Johnson and Daub, "Organic Reactions," John Wiley and Sons, 1951, Vol. VI, p. 1) has made available a general route to tetrahydroindan-1-ones of established structure and it seemed likely that, under mild conditions, reduction of the double bond could be achieved to furnish the required hexahydro-derivatives. Several isolated instances of such reductions have been reported. Hückel and Schluter (*Ber.*, 1934, **67**, 2107) have claimed the reduction of 4 : 5 : 6 : 7-tetrahydroindan-4-one to the hexahydro-ketone at a palladium catalyst under normal pressure and temperature. More recently Braude and Coles (*J.*, 1952, 1430) have carried out an analogous reduction of 9-oxo-$\Delta^{12}$-decahydrofluorenone with platinic oxide, whilst at 75°/70 atm. the hydrogenation of the αβ-ethylenic bond in 6 : 7-dihydronaphtho(1′ : 2′-4 : 5)indan-1-one has been claimed (Johnson and Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1362). Insufficient information was available, however, as to the preparative value of such a method for larger quantities of the saturated ketones required in connection with other work, and the investigation of this point is described below.

A number of tetrahydroindanones were synthesised by Stobbe condensation between the requisite ketone and diethyl succinate, ring closure of the resulting half-ester, and then hydrolysis and decarboxylation. The following were thus smoothly obtained : 4 : 5 : 6 : 7-tetrahydro- (Johnson, Davis, Hunt, and Stork, *ibid.*, 1948, **70**, 3022), 4 : 5 : 6 : 7-tetrahydro-6-phenylindan-1-one, 6 : 7-dihydro- (Johnson, Johnson, and Petersen, *ibid.*, 1945, **67**, 1360), and 4 : 5 : 6 : 7 : 1′ : 2′ : 3′ : 4′-octahydro-4 : 5-benzindan-1-one.

When αβ-unsaturated carbonyl compounds are hydrogenated at a palladium catalyst it has been shown (Weidlich and Meyer-Delius, *Ber.*, 1941, **74**, 1195, 1213) that in alkaline solution 1 : 4-addition occurs followed by ketonisation of the resulting enol to the *trans*-ketone, whilst in acid solution 1 : 2-addition to the double bond takes place to yield a *cis*-ketone (accompanied by the *cis*-hydrocarbon).

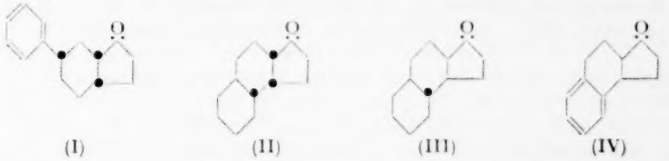



This has been demonstrated where R and R′ are not involved in a ring structure, but since the more stable configuration of the hydroindane nucleus is *cis* (Hückel, Sachs, Yantschulewitsch, and Nerdel, *loc. cit.*) it seemed likely that under either acid or alkaline conditions this form would predominate. This proved to be so and when reduced at a 5% palladium–barium sulphate catalyst in alcohol (with or without the addition of sodium hydroxide or hydrogen chloride), tetrahydroindanone rapidly yielded hexahydroindan-1-one in excellent yield. The derived semicarbazone had m. p. 212° and the oxime m. p. 75—90°. These figures are in good agreement with those given by Hückel *et al.* (*loc. cit.*)

* Part I, *J.*, 1951, 177.

for the same derivatives of a hexahydroindan-1-one (*cis* : *trans* ratio 10 : 1). *cis-trans*-Interconversion has, however, been shown to occur on distillation of hexahydroindan-4-one (Hückel and Doll, *Annalen*, 1936, **526**, 103) and interconversion seems likely in the present instance also.

Under identical conditions (palladium–barium sulphate in methanol) 4 : 5 : 6 : 7-tetrahydro-6-phenyl- and 4 : 5 : 6 : 7 : 1′ : 2′ : 3′ : 4′-octahydro-4 : 5-benzindan-1-one gave the fully reduced ketones in good yield. Tentative assignments of configuration may be made. In the former case, if a *cis*-hydroindane structure is assumed, conformational analysis indicates that a 6-phenyl substituent may be inserted in either the *cis*- or the *trans*-position with respect to $C_{(8)}$-hydrogenation, so that the molecule involves one polar and two equatorial bonds: the alternatives are thus of equal stability. During reduction, however, tetrahydro-6-phenylindanone would be preferentially adsorbed on the catalyst in such a way that the phenyl group would be directed away from the body of the catalyst (cf. Linstead and his co-workers, *J. Amer. Chem. Soc.*, 1942, **64**, 1985; *J.*, 1950, 1431). *cis*-Addition of hydrogen at $C_{(8)}$ and $C_{(9)}$ would then occur, yielding (I). For decahydro-4 : 5-benzindane the *trans-syn-cis*- (II) and the *trans-anti-cis*-conformation (III) are of equal stability, each involving one polar and three equatorial bonds (Johnson, *Experientia*, 1951, p. 315).



(I) (II) (III) (IV)

The ease of reduction in the above cases is in contrast to the findings by Hamlet, Henbest, and Jones (*J.*, 1951, 2652) that similarly constituted 3-alkyl-4 : 5 : 6 : 7-tetrahydroindan-1-ones are resistant to hydrogenation in acetic acid at a palladium catalyst. This result cannot be confirmed in the present case, as tetrahydroindanone has been found to be easily reduced in acetic acid at a 5% palladium–barium sulphate catalyst.

Such reduction of 6 : 7-dihydro-4 : 5-benzindan-1-one was slow and incomplete, leading to a mixture. However, at 80°/80 atm. the required ketone (IV) was easily obtained, though a mixture with the alcohol was formed: the ketone was assayed by 2 : 4-dinitrophenylhydrazone, and the alcohol present reoxidised to the ketone by using the theoretical amount of chromic anhydride. If tetrahydroindan-1-one was hydrogenated under similar high-pressure conditions, no reduction of the ketonic group occurred and hexahydroindanone was obtained in 90% yield.

For the tetrahydroindanones the position of the ethylenic link αβ to the carbonyl group is confirmed by the position of the main band at 2370 Å in the ketone (3950 Å in the dinitrophenylhydrazones and 2650 Å in the semicarbazones; Hamlet, Henbest and Jones, *loc. cit.*; Braude and Coles, *J.*, 1952, 1430). On hydrogenation, a hypsochromic shift is observed of 300 Å in the position of the main bands of the dinitrophenylhydrazones and semicarbazones. The position of these at 3660 Å and 2300 Å respectively is normal for saturated aliphatic ketones (Braude and Jones, *J.*, 1945, 498). With the ketones themselves reduction of the conjugated double bond is marked by the expected disappearance of the high-intensity band at 2370 Å and the appearance of the usual low-intensity carbonyl peak at 2880 Å. The bathochromic shift of 500 Å observed on passage from 4 : 5 : 6 : 7-tetrahydroindanone to 6 : 7-dihydro-4 : 5-benzindanone where extra conjugation with an aromatic nucleus obtains is in line with similar cases recorded by Wilds *et al.* (*J. Amer. Chem. Soc.*, 1497, **69**, 1985). This conjugation is destroyed on hydrogenation and the position of the main band of the 2 : 4-dinitrophenylhydrazone of (IV) is normal for saturated ketones. The presence of the benzene ring in (IV) is confirmed by low-intensity vibrational structure between 2500 and 2750 Å typical of tetrahydronaphthalene (Friedel and Orchin, "Ultra-violet Spectra of Organic Compounds," John Wiley and Sons, New York, 1951). That no reduction of the benzene ring in the ketone (I) had occurred is likewise confirmed by the appearance of absorption due to the phenyl*cyclo*hexane chromophore.

## Experimental

Microanalyses in this and the following paper are by Mr. G. S. Crouch. Light absorptions were measured in EtOH for the ketones and semicarbazones, and in $CHCl_3$ for the 2 : 4-dinitrophenylhydrazones (main band only given).

4 : 5 : 6 : 7-*Tetrahydroindanone.*—Ethyl β-carboxy-α-*cyclo*hexenylpropionate (40 g.) in acetic anhydride (580 ml.) was refluxed with zinc chloride (8 g.) in acetic acid (400 ml.) for 5 hr. under nitrogen. Acetic acid and anhydride were removed *in vacuo* and the residue refluxed for 3 hr. with concentrated hydrochloric acid (100 ml.) in acetic acid (100 ml.). To the residue left after removal of solvent, sufficient sodium hydroxide was added to make the suspension faintly alkaline to litmus, and the whole was extracted with ether. There resulted on distillation a colourless oil, b. p. 83·5—85°/2 mm. (10·9 g.), $n_D^{18}$ 1·5260 (cf. Johnson, Davis, Hunt, and Stork, *loc. cit.*). Absorption max.: ketone 2370 (*E* 12,700), 2 : 4-dinitrophenylhydrazone 3950 (*E* 27,500), semicarbazone 2650 Å (*E* 26,500).

4 : 5 : 6 : 7-*Tetrahydro-6-phenylindanone* [with Dr. E. I. Haiba].—Under the above conditions methyl 4 : 5 : 6 : 7-tetrahydro-3-oxo-5-phenylindane-1-carboxylate (unpublished work) (5 g.) was converted into the *tetrahydro-6-phenylindanone* (2 g.), colourless needles [from light petroleum (b. p. 60—80°)], m. p. 79—80° (Found: C, 84·6; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·5%). Absorption max.: 2370 (*E* 12,750). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in orange-red needles, m. p. 235—236° (Found: C, 64·4; H, 5·3; N, 14·4. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·1; N, 14·3%). Absorption max.: 3940 Å (*E* 33,000).

4 : 5 : 6 : 7 : 1′ : 2′ : 3′ : 4′-*Octahydro*-4 : 5-*benzindan*-1-*one.*—*trans*-α-Decalone (15·2 g.) and diethyl succinate (19 g.) were condensed in presence of potassium *tert.*-butoxide [from potassium (4 g.) and excess of *tert.*-butanol] in the usual way, to yield *ethyl* β-*carboxy*-α-(1-Δ¹-*octahydronaphthyl*)*propionate* as a viscous colourless oil, b. p. 165—169°/0·5 mm. (19·5 g.) (Found: C, 68·4; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·6; H, 8·6%). This (38 g.) was cyclised with zinc chloride–acetic anhydride in acetic acid as above. The resulting *ketone* was obtained as a colourless oil, b. p. 130—132°/0·5 mm. (12·2 g.) (Found: C, 81·9; H, 9·2. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%). Absorption max.: 2390 Å (*E* 13,000).

The 2 : 4-*dinitrophenylhydrazone* crystallised in dark red plates, m. p. 203—204°, from glacial acetic acid (Found: C, 61·7; H, 5·8; N, 14·8. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%). Absorption max.: 3960 Å (*E* 29,300). The *semicarbazone* crystallised from glacial acetic acid in colourless needles, m. p. 265° (decomp.) (Found: C, 68·1; H, 8·5; N, 17·0. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%). Absorption max.: 2660 Å (*E* 26,000).

*Hydrogenation of the Tetrahydroindanones to Hexahydroindanones. General Method.*—The tetrahydroindanone (5 g.) was dissolved in methanol or *iso*propanol (40 ml.) and hydrogenated at a 10% palladium–barium sulphate catalyst (1 g.) at atmospheric temperature and pressure. The time of hydrogen uptake varied from 1 to 5 hr. with different compounds and in every case uptake ceased when one mol. had been absorbed. The crude ketone was assayed by precipitation of the 2 : 4-dinitrophenylhydrazone and weighing of the crude precipitate. In every case 95—98% was present and no significant amount of alcohol appeared therefore to have been produced. Under the above conditions the following were thus obtained.

Hexahydroindanone, a colourless oil, b. p. 72—73/6 mm., $n_D^{25}$ 1·4813. Absorption max.: 2880 Å (*E* 23). The 2 : 4-dinitrophenylhydrazone crystallised from glacial acetic acid in orange yellow plates, m. p. (various batches) variable, 163—165° to 130—140°. All samples, however, contained 17·4—17·6% of nitrogen and showed an absorption peak at 3670 Å (*E* 28,000). The semicarbazone, crystallised from aqueous acetic acid, had m. p. 211—212° (Found: N, 21·6. Calc. for $C_{10}H_{17}ON_3$: N, 21·5%). Absorption max.: 2300 Å (*E* 14,200) (Hamlet, Henbest, and Jones, *loc. cit.*; Part I, *loc. cit.*).

6-*Phenylhexahydroindanone*, crystallising from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 57—60 (Found: C, 83·7; H, 8·0. $C_{15}H_{18}O$ requires C, 84·0; H, 8·4%). Absorption max.: 2090, 2480, 2530, 2585, 2640, 2675 Å (*E* 8250, 132, 181, 218, 166, 155 respectively). The 2 : 4-*dinitrophenylhydrazone* crystallised in orange needles (from glacial acetic acid), m. p. 169—179° (Found: C, 63·8; H, 5·7; N, 14·4. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%) [absorption max.: 3670 Å (*E* 25,000)], and the *semicarbazone* from aqueous acetic acid in colourless plates, m. p. 254—255° (Found: C, 70·7; H, 7·9; N, 15·4. $C_{16}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·5%).

*Decahydro*-4 : 5-*benzindanone*, crystallising from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 58—59° (Found: C, 81·1; H, 10·0. $C_{13}H_{20}O$ requires C, 81·3; H, 10·4%). Absorption max.: 2880 Å (*E* 24). The 2 : 4-*dinitrophenylhydrazone* crystallised from glacial acetic

acid in orange-yellow plates, m. p. 204—206° (Found : C, 61·4; H, 6·6; N, 15·2. $C_{19}H_{24}O_4N_4$ requires C, 61·3; H, 6·5; N, 15·1%). Absorption max. : 3680 Å (*E* 24,000). The *semicarbazone* crystallised from aqueous acetic acid in colourless crystals, m. p. 247—248° (Found : C, 67·7; H, 9·2; N, 17·1. $C_{14}H_{23}ON_3$ requires C, 67·5; H, 9·2; N, 16·9%). Absorption max. : 2300 Å (*E* 14,000).

When the above conditions were applied to 4 : 5 : 6 : 7-tetrahydro-4 : 5-benzindanone uptake of gas was very uneven and incomplete. The resulting material proved to be a mixture. The following conditions were found to be successful (cf. Johnson and Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1362).

4 : 5 : 6 : 7-*Tetrahydro*-4 : 5-*benzindanone*.—6 : 7-Dihydro-4 : 5-benzindan-1-one (Johnson, Johnson, and Petersen, *ibid.*, 1945, **67**, 1360) (9 g.) in *iso*propanol (400 ml.) was hydrogenated in presence of a 5% palladium–barium sulphate catalyst at 80°/80 atm. After remaining 2 hr. under these conditions the autoclave was allowed to cool during some 3 hr., whereafter the contents were worked up in the usual fashion. A mixture (8·9 g.) of alcohol and ketone resulted. The ketonic content was estimated and the mixture then oxidised by the theoretical quantity of chromic anhydride in glacial acetic acid. On working up in the usual way, the *ketone* was obtained as a colourless oil, b. p. 135—140°/6 mm., $n_D^{20}$ 1·5680 (Found : C, 83·2; H, 7·7. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised in orange plates, m. p. 214—215°, from glacial acetic acid (Found : C, 62·3; H, 4·6; N, 15·3. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·9; N, 15·3%). The *semicarbazone* crystallised from dioxan in colourless needles, m. p. 231—232° (Found : C, 68·9; H, 7·0; N, 17·4. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%).

The following absorption max. were recorded. 6 : 7-Dihydro-4 : 5-benzindanone, 2340 (*E* 11,600) and 2970 Å (*E* 16,650) [2 : 4-dinitrophenylhydrazone, 4100 Å (*E* 35,500); semicarbazone, 3260 Å (*E* 32,000)]. 6 : 7 : 8 : 9-Tetrahydro-4 : 5-benzindanone, 2520, 2660, and 2740 Å (*E* 570, 714, 700 respectively) [2 : 4-dinitrophenylhydrazone, 3660 Å (*E* 24,000)]. Phenyl*cyclo*hexane, 2090, 2480, 2530, 2585, 2610, 2640, and 2675 (*E* 7750, 123, 176, 212, 208, 158, and 161 respectively).

The work in this and the following two papers was carried out during the tenure of an I.C.I. Fellowship from the University of London. I also thank Professor W. H. Linnell for his interest and advice throughout.

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## 645. *Perhydroindanes. Part III.** cis-*Hexahydroindane*-1-*carboxylic Acid.*

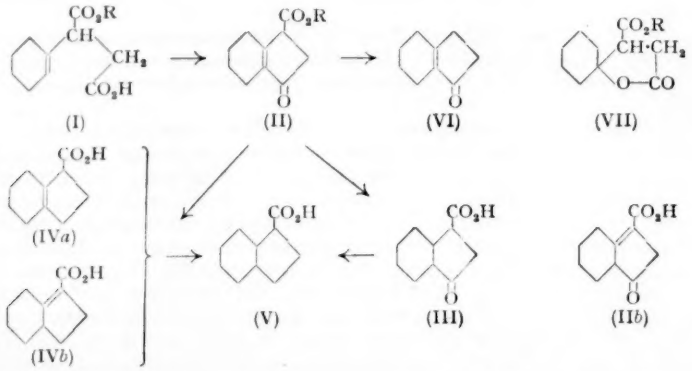
By David W. Mathieson.

Towards a general synthesis of hexahydroindane-1-carboxylic acids, ring closure of the half ester of *cyclo*hexenylsuccinic acid has been examined. Ethyl 4 : 5 : 6 : 7-tetrahydro-3-oxoindane-1-carboxylate (II) thus formed has been reduced to *cis*-hexahydroindane-1-carboxylic acid. With hydrazoic acid this has been converted into the known *cis*-1-aminohexahydroindane.

Three methods have previously been described which could conceivably be used for the synthesis of hexahydroindane-1-carboxylic acids from suitably substituted *cyclo*hexanes. First, ethyl hexahydro-2-oxoindane-1-carboxylate has been obtained by a Dieckmann reaction on ethyl *cyclo*hexane-1 : 2-diacetate (Hückel and Friederich, *Annalen*, 1927, **451**, 132). Secondly, the corresponding 3-oxo-derivative has similarly been made from ethyl 2-ethoxycarbonyl*cyclo*hexylsuccinate (Chatterjee, *J. Indian Chem. Soc.*, 1937, **14**, 419). Thirdly, ring closure of ethyl hydrogen *cyclo*hexenylsuccinate has been described by Johnson, Davis, Hunt, and Stork (*J. Amer. Chem. Soc.*, 1948, **70**, 3021). In all cases, however, the intermediate keto-esters were utilised for final compounds other than the acid required in the present instance. It was decided to investigate the last-named method further, since a large variety of such *cyclo*hexenylsuccinic acids were potentially available

* Part II, preceding paper.

in a single step from the corresponding *cyclo*hexanones by the Stobbe condensation. Reduction of the resulting keto-esters was expected to furnish the hydroindane-1-carboxylic acids.




*cyclo*Hexanone was condensed in presence of potassium *tert.*-butoxide with diethyl succinate (Johnson *et al.*, *loc. cit.*), but the product required extensive fractionation before satisfactory analytical figures could be obtained. When dimethyl succinate was used an unsaturated acid, m. p. **73—74°**, was readily obtained. Its constitution as β-*cyclo*hex-1-enyl-β-methoxycarbonylpropionic acid (**I**; R = Me) follows from the following observations: (*a*) absorption of one mol. of hydrogen to yield, after hydrolysis, *cyclo*hexylsuccinic acid, (*b*) formation of *cyclo*hex-1-enylsuccinic acid on treatment with barium hydroxide, (*c*) absence of *cyclo*hexanone on permanganate oxidation, and (*d*) absence of light absorption at *ca.* 210 mμ in ethanol, a characteristic of the corresponding *cyclo*hexylidene compound.

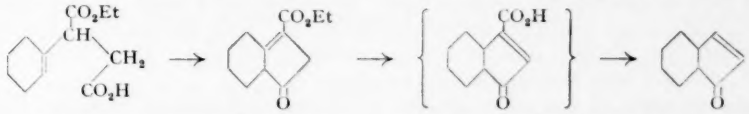
A similar product, m. p. **73·5—74·5°**, has been described by Robinson and Seijo (*J.*, **1941**, 582) as resulting from the condensation of *cyclo*hexanone and dimethyl succinate in presence of sodium methoxide, the constitution assigned by them being that of a methyl paraconate (**VII**; R = Me). Repetition of their work yielded no crystalline fraction insoluble in bicarbonate: it is here that any methyl paraconate would be found. From the fraction soluble in bicarbonate, a product, m. p. **73—74°**, resulted, identical with that obtained when potassium *tert.*-butoxide was used. This compound, moreover, gave a large depression of the melting point on admixture with an authentic specimen of (**VII**), and it seems probable that the material obtained by Robinson and Seijo was (**I**; R = Me). Although initial ring-closure experiments were carried out on this methyl hydrogen ester, it was subsequently found equally satisfactory to utilise the once distilled crude oil which resulted when diethyl succinate was used, since distillation after ring closure sufficed for purification.

The action of various cyclising agents on these half esters is shown in the accompanying Table. The main product was a viscous oil previously assigned the structure (**II***b*; R = Me or Et) (Johnson *et al.*, *loc. cit.*). The light absorption of this unsaturated keto-ester and related compounds, however, suggested that it was ethyl **4 : 5 : 6 : 7**-tetrahydro-**3**-oxoindane-**1**-carboxylate (**II**). This was supported by its chemical properties. Careful

| Substance | Reagent | Products | Yield (%) | Substance | Reagent | Products | Yield (%) |
|---|---|---|---|---|---|---|---|
| I; R = Me | $ZnCl_2$–$Ac_2O$ | II; R = Me | 56—60 | Acid chloride of (I; R = Et) | $SnCl_4$ | II; R = Et | 36 |
| I; R = Et | $ZnCl_2$–$Ac_2O$ | II; R = Et | 55 | | | | |
| I; R = Et | F·$SO_3H$ (room temp.)* | II; R = Et | 60 | Oily fraction (II; R = Me ?) | $ZnCl_2$–$Ac_2O$ | II; R = Me | 20 |
| | | VII; R = H | 20 | | | | |
| I; R = Et | F·$SO_3H$ (100°) | II; R = H | 30 | | | | |
| | | II; R = Et | 25 | | | | |
| | | VI | 5 | | | | |

* Wilson Baker, Coates, and Glockling, *J.*, 1951, 1376.

hydrolysis of (II; R = Et) with barium hydroxide gave an acid, presumably (II; R = H), which on treatment with Brady's reagent yielded the dinitrophenylhydrazone of the starting keto-ester (for similar esterifications of keto-acids, cf. Ansell and Hey, *J.*, 1950, 2874). The acid was unstable, readily losing carbon dioxide at room temperature under a slight vacuum—behaviour identical with that of the acid fraction (II; R = H) isolated



from the fluorosulphonic acid ring closure (Table) and intelligible on the basis of formula (II) which is the vinylogue of a β-keto-acid. A possible alternative course shown above has already been demonstrated in the equilenin series (Johnson, Gutsche, Hirschmann, and Stromberg, *J. Amer. Chem. Soc.*, 1951, **73**, 322). It is ruled out in the present instance since the decarboxylation product of the acid fraction yielded only 4 : 5 : 6 : 7-tetrahydroindanone (VI) and none of the $\Delta^2$-isomer.

| | Ketone * | | 2 : 4-Dinitrophenylhydrazone † | | Semicarbazone * | |
|---|---|---|---|---|---|---|
| | $\lambda_{max.}$ (Å.) | *E* | $\lambda_{max.}$ (Å.) | *E* | $\lambda_{max.}$ (Å.) | *E* |
| (II; R = Me, Et) | 2375 | 10,000 | 3880 | 30,000 | 2670 | 25,500 |
| (III) ..... | 2880 | 21 | 3650 | 24,600 | 2300 | 12,500 |

* In ethanol. † In chloroform.

The light absorption (Table) of (II) and its semicarbazone confirms the presence of an αβ-unsaturated ketone grouping in this material and the values recorded agree with those of the corresponding derivatives of tetrahydroindanone (VI) (Part I, *J.*, 1951, 177; Hamlet, Henbest, and Jones, *J.*, 1951, 2652). The 2 : 4-dinitrophenylhydrazone is, however, anomalous: the main band at 2880 Å lies intermediately between those for the dinitrophenylhydrazones of the saturated hexahydroindanone (3670 Å) (Part II) or (III) (3650 Å) and the conjugated ketone (VI) (3950 Å). Such a value seems not inconsistent with structure (II*b*) where the double bond is conjugated with the ethoxycarbonyl grouping. The situation is similar to that with Hagemann's ester. Infra-red absorption measurements in $CS_2$ solution indicate that the ketone (VI) and the keto-ester (II) show a band at 1702 cm.$^{-1}$ assigned to the αβ-unsaturated keto-group, whilst, in addition, (II) possesses a band at 1735 cm.$^{-1}$ similar to that of *aetio*cholanic esters (1742—1737 cm.$^{-1}$) and assigned therefore to the ethoxycarbonyl group (Jones and Dobriner, *Vitamins and Hormones*, 1949, **7**, 293).

Clemmensen reduction of the unsaturated keto-ester (II; R = Me or Et) yielded an oily mixture of unsaturated acids, probably (IV*a* and *b*), which absorbed one mol. of hydrogen at Adams platinum oxide to give about 75% of a crystalline hexahydroindane-1-carboxylic acid (V), m. p. 88—92°. Several recrystallisations from light petroleum raised the m. p. to 95—96°. By dissolving the oily mixture of unsaturated acids in light petroleum and storage in the refrigerator for several months, a small amount of a crystalline tetrahydroindanecarboxylic acid (IV) was obtained (m. p. 126·5—127°) also produced by bromination of hexahydroindane-1-carboxylic acid followed by removal of the elements of hydrogen bromide. The presence of the double bond was confirmed by quantitative microhydrogenation. This substance showed maximum absorption at 2340 Å (*E* 12,000), a somewhat long wave-length for αβ-unsaturated acids which normally absorb at 2180 Å (Ungnade and Ortega, *J. Amer. Chem. Soc.*, 1951, **73**, 1564) even if allowance is made for strain. The nature of this by-product is obscure, and insufficient was available for further investigation. Its presence in the oily product from the Clemmensen reduction, however, made it impossible to detect absorption at 2180 Å typical of αβ-unsaturated acids.

In presence of palladium, the keto-ester (II; R = Et) yielded hexahydro-3-oxoindane-1-carboxylic acid (III) after hydrolysis. Although the m. p. of this substance and its semicarbazone do not agree with values previously reported (Chatterjee, *loc. cit.*), the light absorption of the ketone and its derivatives is identical with that of hexahydroindan-

1-one (Part II). Clemmensen reduction of (III) moreover yielded the same perhydro-acid (V) as before, the identity being confirmed as follows. Indene-1(3)-carboxylic acid was reduced with hydrogen at Adams platinum oxide. With acetic acid as solvent (Knowles, Kuck, and Elderfield, *J. Org. Chem.*, 1942, **7**, 377) uptake of hydrogen proceeded sluggishly but in ethyl alcohol occurred smoothly in two stages, first to give indane-1-carboxylic acid and then to saturate the benzene ring. In presence of a small amount of hydrogen chloride, simultaneous reduction and esterification took place and ethyl hexahydroindane-1-carboxylate was distilled directly from the reaction mixture. Hydrolysis yielded the free acid, identical with that synthesised as above.

By the principle of one-sided addition of hydrogen (Linstead, Doering, Davis, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985; Linstead and Whetstone, *J.*, 1950, 1431), hydrogenation of the indane nucleus under such conditions should yield a *cis*-perhydro-material. The concept of catalyst hindrance suggests that the carboxyl group would be *trans* to the hydrogen atom at $C_{(8)}$. Such conclusions are likewise reached by consideration of (IV). Thus, as with isolated double bonds, the catalytic addition of hydrogen to C:C $\alpha\beta$ to a carbonyl function proceeds mainly in *cis*-fashion (cf., *inter al.*, Weidlich and Meyer-Delius, *Ber.*, 1941, **74**, 1195, 1213) and in the present case involving (IV*a* or *b*) would occur so as to produce from such relatively planar unsaturated structures that form of lowest energy, a *cis*-hydroindane. Under such conditions of addition the carboxyl group is of necessity *trans* to the 8-hydrogenation.

These predictions have been partly confirmed by the degradation of hexahydroindane-1-carboxylic acid, with sodium azide, to *cis*-1-aminohexahydroindane. The benzoyl derivative had the melting point recorded by Hückel, Sachs, Yantschulewitsch, and Nerdel (*Annalen*, 1935, **518**, 155).

## Experimental

β-cyclo*Hex*-1-*enyl*-β-*methoxycarbonylpropionic Acid* (I).—To a solution of potassium *tert.*-butoxide (from potassium, 42 g., and dry *tert.*-butanol, 900 ml.) were added *cyclo*hexanone (117 g.) and dimethyl succinate (146 g.), the mixture being refluxed under nitrogen for 20 min. and then cooled in ice. Concentrated hydrochloric acid (150 ml.) in ice-water (150 ml.) was slowly added so that the temperature did not exceed 20°. Excess of *tert.*-butanol was removed on the steam-bath *in vacuo* and the residue extracted with ether. The acid fraction was isolated in the usual way with 10% aqueous sodium carbonate. There resulted a viscous residue, b. p. 138—140°/0·3 mm. (118 g., 81%). After a few days at room temperature this solidified and was crystallised from light petroleum (b. p. 60—80°). The total solid (A) weighed 60 g. (m. p. 69—72°). A specimen recrystallised several times from light petroleum (b. p. 60—80°) had m. p. 73—74° [Found: C, 62·3; H, 7·6%; equiv., 211; microhydrogenation (Pd–EtOH) 1·0 C:C. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%; equiv., 212]. From the mother-liquors on removal of solvent there resulted a viscous oil (B), b. p. 115—130°/0·1 mm. (45 g.), from which no crystalline material could be isolated.

Fraction (A) was hydrogenated at palladium–charcoal in ethanol, and the product was refluxed for 30 min. with 3N-sodium hydroxide, whereafter acidification yielded *cyclo*hexylsuccinic acid crystallising from water in colourless needles, m. p. 145—146° (Johnson *et al.*, *loc. cit.*, cite m. p. 145—146°).

Fraction (B) on microhydrogenation revealed the presence of 1·1 double bond. Hydrolysis of the resulting material yielded *cyclo*hexylsuccinic acid, m. p. 143—145°.

With barium hydroxide at room temperature fraction (B) yielded a mixture of acids from which *cyclo*hexylidenesuccinic acid, m. p. 193° (decomp.), was isolated by crystallisation from water (Johnson *et al.*, *loc. cit.*, cite m. p. 179—180°) (Found: C, 60·9; H, 7·3. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·5%). This acid absorbed 1 mol. of hydrogen in presence of 10% palladised carbon, to yield *cyclo*hexylsuccinic acid, m. p. 144—145°.

Potassium permanganate (3·19 g.) in water (180 ml.) was added during 2½ hr. with stirring at 0° to fraction (B) (2·2 g.) in a solution of sodium carbonate (2·13 g.) in water (10 ml.). Steam-distillation of the mixture into a solution of 2 : 4-dinitrophenylhydrazine yielded *cyclo*hexanone 2 : 4-dinitrophenylhydrazone (0·63 g.), m. p. and mixed m. p. 159—160°.

Similar treatment of the crystalline fraction (A) yielded no *cyclo*hexanone. Fraction (A) is thus β-cyclo*hex*-1-*enyl*-β-*methoxycarbonylpropionic acid*, whilst fraction (B) appears to contain in addition some of the *cyclo*hexylidene analogue [cf. ring closure experiment (d) below].

β-Ethoxycarbonyl-β-*cyclo*hex-1-enylpropionic acid was synthesised as described by Johnson *et al.* (*loc. cit.*).

*Ring-closure Experiments.*—(a) *Zinc chloride–acetic anhydride.* The half ester (I; R = Me) (42 g.) in freshly distilled acetic anhydride (300 ml.) was refluxed (under nitrogen) with acetic acid (300 ml.) containing fused zinc chloride (6 g.) for 4½ hr. Excess of anhydride and acid were removed *in vacuo* and the residue poured into water which was then made alkaline with sodium carbonate. A dried ethereal extract on evaporation gave *methyl* **4 : 5 : 6 : 7-*tetrahydro*-3-*oxo*-*indane*-1-*carboxylate*** (II; R = Me) (22 g.), b. p. 112—115°/0·2 mm., $n_D^{21}$ 1·5056 (Found : C, 68·3; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2%). The **2 : 4-*dinitrophenylhydrazone***, m. p. 195—196°, crystallised from xylene in orange plates (Found : C, 54·9; H, 4·8; N, 15·0. $C_{17}H_{18}O_6N_4$ requires C, 54·6; H, 4·8; N, 15·0%). The ***semicarbazone*** crystallised from methanol in colourless needles, m. p. 210—210·5° (Found : C, 57·5; H, 6·9; N, 16·7. $C_{12}H_{17}O_3N_3$ requires C, 57·4; H, 6·8; N, 16·7%).

β-Ethoxycarbonyl-β-*cyclo*hex-1-enylpropionic acid (I; R = Et) under similar conditions gave a 55% yield of ***ethyl* 4 : 5 : 6 : 7-*tetrahydro*-3-*oxoindane*-1-*carboxylate*** (II; R = Et), a light yellow oil, b. p. 104—110°/0·1 mm., $n_D^{20}$ 1·5028 (Found : C, 69·5; H, 7·4. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The **2 : 4-*dinitrophenylhydrazone*** crystallised from acetic acid in orange plates, m. p. 171—172° (Found : C, 55·4; H, 5·2; N, 14·6. $C_{18}H_{20}O_6N_4$ requires C, 55·6; H, 5·2; N, 14·3%). The ***semicarbazone*** crystallised in colourless needles (from methanol), m. p. 192—193° (Found : C, 58·9; H, 7·2; N, 16·0. $C_{13}H_{19}O_3N_3$ requires C, 58·9; H, 7·2; N, 15·9%). The alkaline mother-liquors on acidification yielded an unsaturated acid crystallising from water in colourless needles, m. p. 144—147° (Found : equiv., 99) (Johnson *et al.*, *loc. cit.*, cite m. p. 145—146° for *cyclo*hex-1-enylsuccinic acid).

Fraction B (p. 3254) (12 g.) was treated as described above with acetic anhydride (100 ml.) and zinc chloride (2 g.) in acetic acid (100 ml.). There resulted a neutral fraction (2·2 g., 20%), b. p. 125—127°/0·6 mm., $n_D^{20}$ 1·5070, which readily gave the 2 : 4-dinitrophenylhydrazone and semicarbazone of the keto-ester (II; R = Me).

(b) *Fluorosulphonic acid.* (i) Freshly distilled fluorosulphonic acid (40 ml.) was added with stirring to the half ethyl ester (I; R = Et) (22 g.) at 0—5° (ice-bath). After 6 hr. at room temperature the mixture was poured on ice, then separated into acid and neutral fractions with 10% sodium carbonate solution. From the neutral product (II; R = Et) (13·4 g.), b. p. 107—110°/0·1 mm., a 2 : 4-dinitrophenylhydrazone, m. p. 171—172°, was obtained giving no depression with a specimen isolated as in (a) above. The acid fraction (4·8 g.) was extracted with successive (100 ml.) portions of benzene, to yield colourless needles (2·25 g.), m. p. 176—180° (recrystallised from water : m. p. 186—187°). This did not depress the m. p. of the paraconic acid (VII; R = H) synthesised by Johnson, Davis, Hunt, and Stork's method.

(ii) Fluorosulphonic acid (20 ml.) was added as above to the half ester (I; R = Et) (11 g.), and the whole then warmed on the steam-bath for 40 min. After working up in the usual way there was obtained a neutral fraction (3·6 g.) which gave 4 : 5 : 6 : 7-tetrahydroindanone, b. p. 80—82°/0·2 mm. (0·3 g.), and the keto-ester (II; R = Et), b. p. 114—116°/0·2 mm. (3 g.). Both were identified as their 2 : 4-dinitrophenylhydrazones. The acid fraction (II; R = H) (3·5 g.) proved to be a dark brown oil which gave the 2 : 4-dinitrophenylhydrazone, m. p. 195—196° (from methanol) of (II; R = Me), and the corresponding derivative, m. p. 171—172° (from ethanol) (II; R = Et).

The acid fraction (1·4 g.) was decarboxylated by warming it gently under reduced pressure. When evolution of gas was complete the residue was distilled, to give a colourless oil (0·26 g.), b. p. 80—85°/0·5 mm. The 2 : 4-dinitrophenylhydrazone crystallised in dark red needles, m. p. 239°, from ethanol. The semicarbazone crystallised in pale yellow needles, m. p. 244—245° (placed in bath at 237°), from dilute acetic acid. Neither derivative gave a depressed m. p. on admixture with the corresponding derivative of 4 : 5 : 6 : 7-tetrahydroindanone (Mathieson, *J.*, 1951, 177).

(c) *Acid chloride–stannic chloride ring closure* [with Dr. E. I. Haiba]. Thionyl chloride (13 ml.) was added dropwise with stirring at 0° to a mixture of the half ester (I; R = Et) (20 g.) and pyridine (9 g.) in dry ether (140 ml.). The whole was then kept at room temperature for 3 hr. Precipitation of pyridine hydrochloride was completed by the addition of a further quantity of ethereal hydrogen chloride, and the precipitate was filtered off. Evaporation yielded the acid chloride of (I; R = Et) as a colourless viscous oil, b. p. 124—128°/2 mm. (13 g.). This was then added at −7° to −10° to ethylene dichloride (18 ml.) and stannic chloride (15 g.), and after 1 hr. the mixture was allowed to attain room temperature during 10 hr. Ice was then added. Ether-extraction gave a dark brown oil which was refluxed in

collidine (20 g.) for 3 hr. under nitrogen. After acidification with dilute hydrochloric acid the keto-ester was extracted with ether; it had b. p. 114—116°/0·3 mm., $n_D^{20}$ 1·5070 (6·5 g.).

Ethyl 4 : 5 : 6 : 7-tetrahydro-3-oxoindane-1-carboxylate (1·6 g.) in ethanol (10 ml.) was shaken for 14 hr. with barium hydroxide (1·3 g.) in water (50 ml.). The precipitated barium salts were filtered off, suspended in water at 0°, and covered with ether. Dilute hydrochloric acid was then added dropwise with vigorous shaking. From the dried ethereal layer a light brown gum (90 mg.) was obtained which gave the dinitrophenylhydrazone, m. p. 169—171°, of (II; R = Et) on treatment with Brady's reagent in ethanol. When the flask containing the above gum was gently evacuated at 20° vigorous evolution of carbon dioxide occurred. Treatment of the residue with Brady's reagent in ethanol yielded the tetrahydroindanone 2 : 4-dinitrophenylhydrazone (143 mg.), m. p. 239—242°.

*Hexahydro-3-oxoindane-1-carboxylic Acid* (III).—The keto-ester (II; R = Et) (1 g.) in ethanol (10 ml.) was shaken with hydrogen in presence of 5% palladised strontium carbonate (1 g.), 120 ml. being absorbed in 18 hr. Evaporation of the solvent gave a viscous gum, hydrolysed by 20% sodium hydroxide to a keto-acid (600 mg.), m. p. 149—150° (from benzene–light petroleum) (Chatterjee, *loc. cit.*, cites m. p. 136°) (Found : C, 66·4; H, 7·9. Calc. for $C_{10}H_{14}O_3$ : C, 66·0; H, 7·7%).

Treatment of the keto-acid with Brady's reagent in methanol gave *methyl hexahydro-3-oxoindane-1-carboxylate* 2 : 4-*dinitrophenylhydrazone*, crystallising from ethyl acetate in yellow plates, m. p. 196—197° (Found : C, 54·2; H, 5·5; N, 14·7. $C_{17}H_{20}O_6N_4$ requires C, 54·3; H, 5·3; N, 14·9%). All keto-acids described in the present paper suffer such simultaneous esterification when treated with 2 : 4-dinitrophenylhydrazine in sulphuric acid–alcohol solution. The semicarbazone crystallised from *iso*propyl alcohol in colourless needles, m. p. 240—241° (decomp.) (Chatterjee, *loc. cit.*, cites 220°) (Found : C, 55·3; H, 7·3; N, 17·4. Calc. for $C_{11}H_{17}O_3N$ : C, 55·2; H, 7·1; N, 17·6%).

*Tetrahydroindane-1-carboxylic Acid* (IV).—(i) Zinc wool (35 g.), amalgamated by being shaken for 30 min. with mercuric chloride (3 g.) in concentrated hydrochloric acid (3 ml.) and water (100 ml.), was covered with 50% hydrochloric acid (100 ml.) and to this was added the ester (II; R = Et) (12·5 g.) in acetic acid (40 ml.). The mixture was refluxed for 10 hr., with occasional additions of hydrochloric acid (5 ml.). From the cold diluted mixture all organic matter was removed by ether-extraction, and the residue left on evaporation freed from acetic acid on the steam-bath under reduced pressure. The brown oil was purified *via* the sodium salt, to give 8·8 g. of acid material. This partly solidified and the solid material (715 mg.) was separated by trituration with ether at −70°. It crystallised from benzene–ethanol in colourless needles, m. p. and mixed m. p. 185—186° [for the paraconic acid (VII; R = H) see Johnson *et al.*, *loc. cit.*]. The oil remaining was fractionated, to yield a colourless oil, b. p. 103—106°/0·1 mm., $n_D^{20}$ 1·5100 (4·7 g.), unsaturated to bromine in carbon tetrachloride and 1% potassium permanganate in acetone. It gave no ketonic reactions. A refractionated sample had b. p. 112—113°/1 mm., $n_D^{20}$ 1·5097 (Found : C, 72·5; H, 8·7%; equiv., 165. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%; equiv., 166). The above oil (1·5 g.) in light petroleum (b. p. 40—60°) (35 ml.) was allowed to remain in the refrigerator for several months. A colourless crystalline acid (120 mg.), m. p. 125—126°, was thus obtained, identical with a sample obtained below.

*Bromination of Hexahydroindane-1-carboxylic Acid.*—The acid (3 g.), bromine (1·2 ml.), and phosphorus trichloride (0·5 ml.) were heated together in a sealed tube on the steam-bath for 3 hr. The resulting dark brown gum was refluxed in collidine (8 ml.) under nitrogen for 3 hr. and then poured into hydrochloric acid. Ether-extraction gave an *acid* fraction (?IV) (400 mg.) as a brown gum which slowly solidified, crystallising from light petroleum (b. p. 40—60°) as colourless needles, m. p. 126·5—127° [Found : C, 72·1; H, 8·3%; microhydrogenation (Pt in EtOH), 1·0 C:C. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%].

*Hexahydroindane-1-carboxylic Acid.*—(i) The above oily acid (IV) (1·65 g.) was hydrogenated in glacial acetic acid (15 ml.) at Adams platinum oxide (140 mg.) : 250 ml. hydrogen were absorbed in 90 min. Evaporation gave a gum (1·66 g.) which solidified to colourless needles, m. p. 81—90°. Recrystallised from light petroleum (b. p. 60—80°) there resulted colourless needles of hexahydroindane-1-carboxylic acid, m. p. 88—92° (1·3 g.). On repeated crystallisation a sample had m. p. 94—95° (Found : C, 71·5; H, 9·7%; equiv., 167. Calc. for $C_{10}H_{16}O_2$ : C, 71·5; H, 9·5%; equiv., 168). The p-*toluidide* crystallised in colourless needles (from benzene), m. p. 189—190° (Found : C, 79·5; H, 9·2; N, 5·4. $C_{17}H_{23}ON$ requires C, 79·4; H, 9·0; N, 5·5%). The p-*bromophenacyl* ester crystallised from methanol in plates, m. p. 115° (Found : C, 59·2; H, 5·6; Br, 21·7. $C_{18}H_{21}O_3Br$ requires C, 59·2; H, 5·8; Br, 21·9%).

(ii) Hexahydro-3-oxoindane-1-carboxylic acid (1 g.), treated with amalgamated zinc (3 g.)

as described above, gave a colourless oil (200 mg.) which slowly solidified. Crystallised from light petroleum (b. p. 60—80°), colourless needles were obtained having m. p. 94—95°, alone or mixed with a sample from (i).

(iii) (cf. Knowles, Kuck, and Elderfield, *loc. cit.*). Indene-1(3)-carboxylic acid (5 g.) (Courtot, *Ann. Chim.*, 1915, **4**, 58, 82) in ethanol (75 ml.) was hydrogenated in presence of Adams platinum oxide (500 mg.) and 3 drops of concentrated hydrochloric acid. Uptake of 1 mol. occurred in 30 min., followed by a slower uptake (6 hr.) of a further 3 mols. Removal of solvent yielded a colourless oil which was dissolved in ether and washed with 5% sodium carbonate solution. The neutral fraction, *ethyl hexahydroindane-1-carboxylate* (5·2 g., 99%) had b. p. 106—108°/0·5 mm., $n_D^{17}$ 1·4782 (Found : C, 73·5; H, 10·4%; sap. equiv., 196. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·2%; sap. equiv., 196).

The ester (5 g.) was refluxed for 4 hr. with potassium hydroxide (4·4 g.) in water (45 ml.) and methanol (20 ml.). Precipitation of the acid with hydrochloric acid gave 4·2 g., crystallising from light petroleum (b. p. 60—80°) in colourless needles, m. p. 90—93°. The *p*-toluidide had m. p. 189—190° (from benzene). Mixed m. p.s of this acid and its toluidide with the corresponding substances synthesised from *cyclo*hexanone gave no depression.

When hydrochloric acid was omitted from the above catalytic reduction no ester was isolated and the product consisted solely of hexahydroindane-1-carboxylic acid. No difference in the rate of hydrogen uptake with or without the addition of hydrogen chloride was observed (cf. Brown, Durand, and Marvel, *J. Amer. Chem. Soc.*, 1936, **58**, 1594); the purity of the indenecarboxylic acid used, however, had a marked influence on the speed of reduction.

cis-1-*Aminohexahydroindane.*—Hexahydroindane-1-carboxylic acid (m. p. 94—95°) (0·88 g.) was dissolved in chloroform (25 ml.), and concentrated sulphuric acid (10 ml.) was added. With stirring, sodium azide (0·5 g.) was added gradually so that the temperature remained at 20—25°. After 30 min. at 50° the mixture was poured on to ice, and any non-basic fraction extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with ether, to yield a base (0·7 g., 99% conversion). This amine (0·35 g.) was benzoylated (Schotten–Baumann), to give *cis*-1-benzamidohexahydroindane (0·42 g., 70%), crystallising from acetone in colourless needles, m. p. 183·5—184°. Hückel, Sachs, Yantschulewitsch, and Niederl (*loc. cit.*) cite m. p. 183—184°.

Infra-red spectra were very kindly determined by Dr. A. E. Kellie of The Courtauld Institute of Biochemistry.

School of Pharmacy, University of London, W.C.1. [*Received, June 27th,* 1953.]

## 646. *A Synthesis of Indane-1-carboxylic Acids.*

By W. H. Linnell, David W. Mathieson, and D. T. Modi.

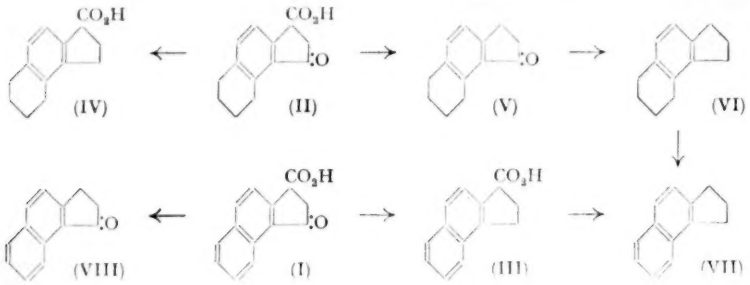
Ring closure of β-naphthyl- and 1 : 2 : 3 : 4-tetrahydro-6-naphthylsuccinic acid, followed by Clemmensen reduction of the intermediate γ-keto-acids, has been shown to lead to 4 : 5-benzindane-1-carboxylic acid and its 1′ : 2′ : 3′ : 4′-tetrahydro-derivative respectively.

As part of a scheme for the synthesis of derivatives of hexahydroindane considered as fragments of the complete steroid nucleus, a general method of preparation of the aromatic derivatives, indane-1-carboxylic acids, was sought. The route described below involves the synthesis and ring closure of various arylsuccinic acids which may be readily prepared from the corresponding aromatic aldehydes. Its utility was first checked by using phenylsuccinic acid itself : ring closure with fluorosulphonic acid (Baker, Coates, and Glockling, *J.*, 1951, 1376) yielded the known 3-oxoindane-1-carboxylic acid. Clemmensen reduction furnished a good yield of indane-1-carboxylic acid (Knowles, Kuck, and Elderfield, *J. Org. Chem.*, 1942, **7**, 377).

The method was next applied to 2-naphthylsuccinic acid and 1 : 2 : 3 : 4-tetrahydronaphthyl-6-succinic acid which were synthesised by standard methods (*Org. Synth.*, 1941, **1**, 451; 1950, **30**, 83). 2-Naphthaldehyde was condensed with ethyl cyanoacetate or

diethyl malonate; the products added hydrogen cyanide smoothly, and subsequent hydrolysis yielded β-naphthylsuccinic acid. 1 : 2 : 3 : 4-Tetrahydro-6-naphthaldehyde (obtained by a Gattermann reaction on tetralin) similarly gave the tetrahydro-analogue.

In contrast to experience with phenylsuccinic acid, intramolecular acylation could not be satisfactorily accomplished under Friedel–Crafts conditions and the reagent of choice was anhydrous hydrogen fluoride: this gave an excellent yield of (I) and (II) after 24




hours' condensation at room temperature. Fluorosulphonic acid gave equally satisfactory yields but presented more difficulties in isolation of the product. Clemmensen reduction gave the corresponding 4 : 5-benz- and 1′ : 2′ : 3′ : 4′-tetrahydro-4 : 5-benz-indane-1-carboxylic acids (III) and (IV).

That the constitutions assigned are correct was shown by the following reactions. (i) Nitric acid oxidation of (II) gave benzene-1 : 2 : 3 : 4-tetracarboxylic acid identified as its tetramethyl ester; (ii) decarboxylation of (II) gave the hitherto unknown 1′ : 2′ : 3′ : 4′-tetrahydro-4 : 5-benzindan-3-one (V) which on Clemmensen reduction yielded the known 1′ : 2′ : 3′ : 4-tetrahydro-4 : 5-benzindane (VI) (Arnold and Barnes, *J. Amer. Chem. Soc.*, 1943, **65**, 2393); (iii) dehydrogenation of (VI) furnished 4 : 5-benzindane (VII) (Kruber, *Ber.*, 1932, **65**, 1382); (iv) decarboxylation of (I) gave 3-oxo-4 : 5-benzindane (VIII) (*idem, loc. cit.*); (v) decarboxylation of (III) gave 4 : 5-benzindane (VII). The direction of ring closure is thus in accord with many analogies. Attempts were made to extend these reactions to 6-hydroxy-2-naphthylsuccinic acid without success. Thus, although 6-methoxy-2-naphthoic acid was smoothly converted into the corresponding aldehyde by McFadyen and Stevens's method (*J.*, 1936, 584) and this was further converted into 6-hydroxy-2-naphthylsuccinic acid, ring closure proved abortive under all conditions tried.

## Experimental

*Indane-1-carboxylic Acid.*—3-Oxoindane-1-carboxylic acid (2·5 g.) in acetic acid (75 ml.) was refluxed for 8 hr. with amalgamated zinc (20 g.) and concentrated hydrochloric acid (100 ml.). After working up in the usual way, there resulted an acid (1·4 g.) crystallising from water in colourless needles, m. p. 55—56°. The *p-toluidide* crystallised from light petroleum (b. p. 80—100°) in stout needles, m. p. 162—163° (Found: C, 81·2; H, 6·9; N, 5·5. $C_{17}H_{17}ON$ requires C, 81·3; H, 6·8; N, 5·6%). Neither the acid nor its toluidide depressed the m. p. of samples produced by hydrogenation of indene-1(3)-carboxylic acid (Knowles, Kuck, and Elderfield, *loc. cit.*).

1 : 2 : 3 : 4-*Tetrahydro-6-naphthaldehyde.*—Dry tetralin (33 g., 0·25 mole), cuprous chloride (3·7 g., 0·02 mole), and dry benzene (150 ml.) were stirred while finely powdered aluminium chloride (33·6 g., 0·25 mole) was added. Separate streams of dry hydrogen chloride and carbon monoxide were then led into the mixture at 50° for 7 hr. The whole was cooled and poured on ice, and steam-distilled. The distillate was extracted with ether, and the extract dried and evaporated. After an initial fraction consisting of unchanged tetralin there was obtained the required aldehyde, b. p. 117—120°/4 mm. (8·5 g.). The semicarbazone had m. p. 221° in agreement with Newman and Zahn (*J. Amer. Chem. Soc.*, 1943, **65**, 1098). The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol in orange plates, m. p. 222° (Found: C, 59·7; H, 4·9; N, 16·4. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

*Ethyl α-Cyano-1 : 2 : 3 : 4-tetrahydro-6-naphthylmethyleneacrylate.*—Piperidine (0·5 ml.) was

added to a mixture of the above aldehyde (11 g.) and ethyl cyanoacetate (8 g.). Heat was evolved and the mixture was held at 100° for 5 min. On cooling, the whole solidified. A portion crystallised from ethanol in pale buff needles, m. p. 62° (Found: C, 75·6; H, 6·9; N, 5·6. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%). The main bulk was carried forward to the next stage.

1 : 2 : 3 : 4-*Tetrahydro-2-naphthylsuccinic Acid.*—The above crude *cyanoacrylate* was dissolved in ethanol (14 ml.) and on addition of sodium cyanide (7 g.) in water (14 ml.) an exothermic reaction ensued. The mixture was kept at 65° for 30 min., cooled, and acidified, a viscous brown oil resulting. The upper aqueous layer was decanted and the bottom layer refluxed with concentrated hydrochloric acid (250 ml.) for 8 hr. The semisolid mass thus formed was triturated with chloroform (3 × 75 ml.), to yield 9·9 g. of the required *acid*, crystallising from 20% aqueous ethanol in colourless plates, m. p. 200° (Found: C, 67·5; H, 6·6%; titration equiv., 125. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%; equiv., 124).

The *dimethyl* ester had b. p. 250°/10 mm. (bath-temp.), m. p. 42° (Found: C, 69·2; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%).

1′ : 2′ : 3′ : 4′-*Tetrahydro-3-oxo-4* : 5-*benzindane-1-carboxylic Acid.*—(a) *By means of hydrogen fluoride.* This reagent was most conveniently handled in "Polythene" ware. To the acid, placed in a narrow-necked screw-capped bottle, liquid anhydrous hydrogen fluoride was added, then the cap was firmly screwed down. Under these conditions the mixture could be safely kept almost indefinitely without evaporation and the use of thin-walled bottles made it possible to observe the contents fairly readily. Such bottles have been in almost constant use for over a year without apparent deterioration. In working up, the reagent is easily evaporated on the steam-bath from a "Polythene" beaker. The above tetrahydronaphthylsuccinic acid (15 g.), dissolved in anhydrous hydrogen fluoride (150 ml.), was kept for 24 hr. Evaporation left a residue (13·2 g.) which crystallised from ethanol–light petroleum (b. p. 100—120°) in stout plates, m. p. 182°. The *semicarbazone* crystallised from aqueous acetic acid in pale yellow plates, m. p. 248° (Found: C, 62·6; H, 6·0; N, 14·2. $C_{15}H_{17}O_3N_3$ requires C, 62·7; H, 5·9; N, 14·6%). The 2 : 4-*dinitrophenylhydrazone* of the *ethyl* ester, crystallised from acetic acid, had m. p. 194° (Found: C, 60·3; H, 5·0; N, 12·8. $C_{22}H_{22}O_8N_4$ requires C, 60·3; H, 5·0; N, 12·8%). The *oxime* crystallised from 50% aqueous alcohol in plates, m. p. 241° (decomp.) (Found: N, 5·7. $C_{14}H_{15}O_3N$ requires N, 5·7%).

(b) *By means of fluorosulphonic acid.* The succinic acid (1 g.) was added to fluorosulphonic acid (8 ml.), and the resulting solution warmed to 100° for 20 min., then poured on ice-water. The product was extracted with ether, to yield the required compound (0·9 g.), crystallising from ethanol–light petroleum in plates, m. p. 182°.

*Oxidation of* 1′ : 2′ : 3′ : 4′-*Tetrahydro-3-oxo-4* : 5-*benzindane-1-carboxylic Acid.*—The keto-acid (1 g.) was refluxed for 180 min. with concentrated nitric acid (15 ml.), a further 15 ml. being added after 90 min. Evaporation left a residue of benzene-1 : 2 : 3 : 4-tetracarboxylic acid which crystallised from ether–light petroleum (b. p. 100—120°) in prisms, m. p. 233—235° (Smith, *J. Amer. Chem. Soc.*, 1933, **55**, 4305, cites m. p. 238°). The tetramethyl ester crystallised from methanol in plates, m. p. 132—133° (*idem*, *loc. cit.*, gives m. p. 133—135°).

1′ : 2′ : 3′ : 4′-*Tetrahydro-4* : 5-*benzindan-3-one.*—The keto-acid (3 g.) in quinoline (30 ml.) was heated at 240° with copper bronze (3 g.). When evolution of gas had ceased (25 min.) the mixture was cooled, filtered, and diluted with four times its volume of ether. Quinoline was removed by repeated shaking with 50% hydrochloric acid, and any unchanged starting material with 10% aqueous sodium hydroxide. The residue on evaporation of the ether proved to be an oily ketone which gave an oily oxime, but the 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in fine red plates, m. p. 278° (Found: C, 62·3; H, 4·5; N, 15·2. $C_{19}H_{16}O_4N_4$ requires C, 62·3; H, 4·9; N, 15·3%).

1′ : 2′ : 3′ : 4′-*Tetrahydro-4* : 5-*benzindane.*—The above ketone (2·9 g.) in toluene (10 ml.) was refluxed for 16 hr. with amalgamated zinc (10 g.) and concentrated hydrochloric acid (17·5 ml.). On cooling, the whole was extracted with ether and the organic layer evaporated, to give the required hydrocarbon as a colourless oil, b. p. 110°/7 mm. (Found: C, 91·2; H, 8·7. Calc. for $C_{13}H_{16}$: C, 90·8; H, 9·3%).

4 : 5-*Benzindane.*—The above tetrahydro-derivative (1 g.) was heated with a 30% palladium–charcoal for 6 hr. at 265—270°. The residual oil obtained on extraction with ether furnished a picrate, m. p. 108—110° (Kruber, *Ber.*, 1932, **65**, 1382, cites m. p. 109—110°).

1′ : 2′ : 3′ : 4′-*Tetrahydro-4* : 5-*benzindane-1-carboxylic Acid.*—1′ : 2′ : 3′ : 4′-Tetrahydro-3-oxo-4 : 5-benzindane-1-carboxylic acid (2 g.) in toluene (5 ml.) was refluxed for 17 hr. with amalgamated zinc (5 g.) and concentrated hydrochloric acid (12 ml.). When worked up by the usual pro-

cedure *via* the sodium salt, the required *acid* was obtained, crystallising from 80% aqueous acetic acid in small colourless plates, m. p. 128—129° (1·5 g.) (Found: C, 77·3; H, 7·3. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·4%).

*2-Naphthylsuccinic Acid.*—(*a*) 2-Naphthaldehyde (*Org. Synth.*, 1943, **23**, 63) (1·6 g.) in ethanol (2 ml.) was heated with ethyl cyanoacetate (1·1 g.) and piperidine (0·2 ml.). After 3 min.' warming at 100° the mixture was cooled, yielding *ethyl α-cyano-2-naphthylmethyleneacrylate* (1·4 g.), crystallising from ethanol in clusters of pale yellow needles, m. p. 112° (Found: C, 76·7; H, 5·1; N, 5·5. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

Sodium cyanide (0·5 g.) in water (2 ml.) was added to a suspension of ethyl α-cyano-2-naphthylmethyleneacrylate (1·25 g.) in ethanol (5 ml.). After 12 hr. at 65—75° the cooled mixture was acidified, yielding a viscous brown oil. The aqueous layer was decanted and the oil refluxed for 6 hr. with concentrated hydrochloric acid (25 ml.). Trituration of the resulting semi-solid mass with chloroform gave the required substance (125 mg.), m. p. 218°. Evaporation of the chloroform and re-treatment of the residue with concentrated hydrochloric acid, as above, yielded a further 105 mg. (total yield, 230 mg.), crystallising from 10% ethanol in water in colourless plates, m. p. 220° (Found: C, 68·1; H, 4·7%; titration equiv., 119. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%; equiv., 122). The *dimethyl* ester crystallised from light petroleum (b. p. 40—60°) in needles (m. p. 65°) (Found: C, 70·5; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

(*b*) 2-Naphthaldehyde (30 g.) and ethyl malonate (31·5 g.) in dry benzene (90 ml.) were refluxed with piperidine (1 ml.) until no more water was formed (18—24 hr.). The semi-solid ethyl 2-naphthylmethylenemalonate was then isolated by removal of solvent and dissolved in ethanol (600 ml.). Potassium cyanide (13·5 g.) in water (22·5 ml.) was added and the mixture heated to 70—80° for 19 hr. with constant stirring. After cooling, potassium hydrogen carbonate was filtered off and the filtrate acidified. Concentration of the liquors yielded a viscous oil which was refluxed with concentrated hydrochloric acid (650 ml.) for 6 hr. Trituration with chloroform gave the required acid and, from the chloroform layer, a quantity of viscous oil which was reprocessed with concentrated hydrochloric acid as above. The acid (total yield, 11·5 g.) crystallised from water containing 10% of ethanol, in colourless plates, m. p. 220° giving no depression on admixture with a sample synthesised as in (*a*) above.

*3-Oxo-4 : 5-benzindane-1-carboxylic Acid.*—(a) *By means of hydrogen fluoride.* 2-Naphthylsuccinic acid (8 g.) in anhydrous hydrogen fluoride (150 ml.) was kept at room temperature for 24 hr. Evaporation gave a *keto-acid* (6·5 g.), crystallising from 1 : 9 ethanol–water in needles, m. p. 181—182° (Found: Titration equiv., 221. $C_{14}H_{10}O_3$ requires equiv., 226). The *semicarbazone* crystallised from aqueous acetic acid in pale yellow plates, m. p. 235° (Found: C, 63·5; H, 4·8; N, 14·6. $C_{15}H_{13}O_3N_3$ requires C, 63·6; H, 4·6; N, 14·8%). Satisfactory analyses could not be obtained on the keto-acid or its 2 : 4-dinitrophenylhydrazone.

(b) *By means of fluorosulphonic acid.* 2-Naphthylsuccinic acid (0·5 g.) in fluorosulphonic acid (5 ml.) was warmed on the steam-bath for 7 min. After cooling, the mixture was poured on ice-water and extracted with ether. Crystallisation of the residue thus obtained from 1 : 9 ethanol–water gave needles (0·35 g.), m. p. 181—182°, identical with a sample obtained as in (*a*) above.

(c) *By means of aluminium chloride–acid chloride.* To the acid chloride from β-naphthylsuccinic acid (0·5 g.) in dry nitrobenzene (4 ml.) was added aluminium chloride (0·4 g.) in dry nitrobenzene. The mixture was heated at 110° for 30 min., then decomposed with ice-water. Nitrobenzene was removed by steam-distillation and the insoluble non-volatile residue brought into solution by addition of ethanol. After treatment with charcoal and cooling, the keto-acid (0·2 g.) was obtained, having m. p. 182°.

*4 : 5-Benzindan-3-one.*—3-Oxo-4 : 5-benzindane-1-carboxylic acid (0·5 g.) in quinoline (10 ml.) was refluxed with copper bronze for 15 min. The products were isolated as described for the tetrahydro-isomer, to give the required ketone, crystallising from acetic acid in almost colourless prisms, m. p. 100—102°. The oxime had m. p. 174°. (Kruber, *loc. cit.*, cites m. p. 102—103° and 175—176° respectively.)

*4 : 5-Benzindane-1-carboxylic Acid.*—3-Oxobenzindane-1-carboxylic acid (2 g.) in toluene (5 ml.) was refluxed for 18 hr. with amalgamated zinc (5 g.) and concentrated hydrochloric acid (10 ml.). The resultant *acid* formed colourless plates (m. p. 145°; 1·3 g.) from 50% aqueous acetic acid (Found: C, 78·9; H, 5·8. $C_{14}H_{12}O_2$ requires C, 79·3; H, 5·7%). Decarboxylation with copper bronze gave 4 : 5-benzindane (picrate, m. p. 105—107°) identical with that obtained as described above.

*6-Methoxynaphthalene-2-carboxylic Acid.*—To 2-acetyl-6-methoxynaphthalene (Robinson and Rydon, *J.*, 1939, 1394) (60 g.) in dioxan (600 ml.) there was added during 1 hr. a solution

of hypobromite [from bromine (60 ml.), sodium hydroxide (168 g.) and water (800 ml.)]. Saturated sodium metabisulphite solution (100 ml.) was added to destroy the excess of hypobromite, and dioxan and bromoform were removed *in vacuo*. Acidification of the remaining liquors gave the required acid (51 g.), m. p. 212°. (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2835, cite m. p. 212°.) The *ethyl* ester made in the usual manner had m. p. 96°, crystallising from light petroleum (b. p. 60—80°) in colourless plates (Found: C, 73·3; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%).

6-*Methoxy*-2-*naphthaldehyde*.—The above ethyl ester (50 g.) was refluxed with 90% hydrazine hydrate in alcohol (130 ml.) for 7 hr. After cooling, the resulting *hydrazide* (45 g.) was collected and crystallised from ethanol in colourless plates, m. p. 183° (Found: C, 66·2; H, 5·6; N, 13·1. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). It was then dissolved in pyridine (675 ml.), and benzenesulphonyl chloride (48 ml.) added slowly at 0°. Stirring was continued thereafter for 2 hr. After pouring on ice and hydrochloric acid there resulted 67 g. of the *benzenesulphonyl* derivative. Crystallisation from 80% ethanol in water gave plates, m. p. 202° (Found: C, 60·3; H, 4·7; N, 7·9; S, 8·9. $C_{18}H_{16}O_4N_2S$ requires C, 60·6; H, 4·5; N, 7·9; S, 9·0%). This derivative (24 g.) was suspended in ethylene glycol (540 ml.) and heated to 160°, partial dissolution resulting. Anhydrous sodium carbonate (5 equivs.) was then added and after 60 seconds the vigorous reaction was terminated by cautious addition of boiling water. On cooling, the whole was extracted with benzene–ether (1 : 3) and the dried extract evaporated. Recrystallisation of the residue from methanol (charcoal) gave the required aldehyde in yellow prisms (8 g.), m p. 80° (Hudson, *J.*, 1946, 76, gives m. p. 80—81°). The semicarbazone crystallised from acetic acid in colourless plates, m. p. 275° (*idem*, *ibid.*, gives m. p. 277—278°).

*Ethyl* α-*Cyano*-6-*methoxy*-2-*naphthylmethyleneacrylate*.—To the above aldehyde (5·6 g.) in ethanol (6·5 ml.) was added ethyl cyanoacetate (3·4 g.) and piperidine (0·3 ml.), the mixture being warmed on the steam-bath for 2—3 min. The resulting *cyanoacrylate* (5·6 g.) crystallised from light petroleum (b. p. 100—120°) in pale yellow plates, m. p. 122° (Found: C, 72·5; H, 5·3; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·0%).

6-*Hydroxy*-2-*naphthylsuccinic Acid*.—Sodium cyanide (1·2 g.) in water (5 ml.) was added to a suspension of ethyl α-cyano-6-methoxy-2-naphthylmethyleneacrylate (4·6 g.) in ethanol (5 ml.). After several min. at 100° complete solution resulted. Dilute hydrochloric acid was then added, to precipitate a heavy brown oil. This was refluxed with concentrated hydrochloric acid (75 ml.) for 4 hr. On cooling, the resulting *succinic acid* was filtered off (3·7 g.). Crystallisation from water containing a few drops of dilute hydrochloric acid gave the substance in pale buff-coloured plates, m. p. 210° (Found: C, 64·8; H, 4·7%; titration equiv., 136. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%; equiv., 130). Zeisel estimation indicated absence of methoxyl and demethylation must have occurred during the acid hydrolysis of the intermediate dicyano-acid. The *diethyl* ester, prepared by the Fischer–Speier method, was a yellow oil, b. p. 200°/0·5 mm. (bath-temp.) (Found: C, 68·2; H, 6·6. $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·3%).

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## 647. lin-*Poly*-p-*xylylene*. *Part I*. *Intermediates and Polymers of Low Molecular Weight*.

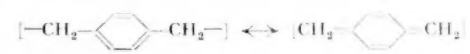
By A. C. Farthing.

Preliminary work is described which was aimed at preparation of *lin*-poly-*p*-xylylene and examination of its structure. Polymer prepared by pyrolysis of *p*-xylene is shown to contain, *inter alia*, low polymers of *p*-xylene, namely, the linear dimer 4 : 4′-dimethyldibenzyl and the cyclic dimer di-*p*-xylylene. Co-distillation with ethylene glycol is used to purify some high-melting methylanthracenes.

Szwarc has described the pyrolysis of alkylated benzenes at low pressures (*J. Chem. Phys.*, 1948, **16**, 128; *Discuss. Faraday Soc.*, 1947, **2**, 39, 46). When *p*-xylene was so treated, the walls of the apparatus where the effluent gasses were cooled became coated with a film of a

white substance of high melting point and low solubility. He concluded that the substance was polymeric and presumably had the structure $[\cdot CH_2 \cdot C_6H_4 \cdot CH_2 \cdot]_n$.

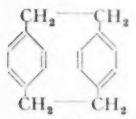
A pyrolysis apparatus similar to Szwarc's was set up and operated by F. Lord and J. S. F. Gill of these Laboratories. At the same time the authors of this series of papers set out to investigate the structure of the polymer and ways of making it other than by the pyrolysis of *p*-xylene. All polymer from the pyrolysis route used in this work was made by Lord and Gill, and their assistance is gratefully acknowledged. The polymer is now shown to be a linear polymer of the *p*-xylylene diradical, or of the labile quinodimethene molecule



and will be called *lin*-poly-*p*-xylylene.

As the most likely structure for the polymer appeared to be that given above, it was decided to examine the polymer obtained by the Wurtz condensation of *p*-xylylene dichloride, since this would be expected to have the same structure. This work is included in Part III (*J.*, 1953, 3270). *p*-Xylylene dichloride and 4-methylbenzyl chloride were made by chlorination of *p*-xylene in carbon tetrachloride, in the presence of traces of phosphoric oxide so as to inhibit the action of traces of metals which catalyse nuclear chlorination and Friedel–Crafts condensations. *p*-Di-2-chloroethylbenzene was made from *p*-xylylene dichloride through the dicyanide to provide an analogous dichloride for the Wurtz reaction.

On storage, crystals appeared on the surface of the films of *lin*-poly-*p*-xylylene made by pyrolysis. The material was extracted with hot chloroform (Soxhlet), the extract being separated by acetone into two fractions. The acetone-insoluble fraction was a very small proportion of the whole and appeared to be homogeneous, having m. p. 285° after recrystallisation from pyridine and acetic acid. In view of its high melting point this fraction was first thought to be an anthracene, possibly a methylated anthracene. 2 : 7-Dimethylanthracene was prepared by the Friedel–Crafts condensation of toluene and methylene dichloride. The purification was tedious but it was found that co-distillation in ethylene glycol provided a very simple technique. The same hydrocarbon is known to be formed by pyrolysis of *p*-xylene at atmospheric pressure (Meyer and Hofmann, *Monatsh.*, 1916, **37**, 681). Accordingly, this preparation was imitated, and 2 : 7-dimethylanthracene isolated readily from the crude product by co-distillation in ethylene glycol. The samples of 2 : 7-dimethylanthracene differed from the acetone-insoluble fraction in melting point and colour reaction with concentrated sulphuric acid. 2 : 3 : 6 : 7- and 1 : 4 : 5 : 8-Tetramethylanthracenes were also prepared and gave the same colour reaction with concentrated sulphuric acid as did the 2 : 7-dimethylanthracene. It was concluded that the acetone-insoluble fraction was probably not a methylated anthracene. Analysis and molecular-weight determination indicated the molecular formula to be $C_{16}H_{16}$, a dimer of the xylylene radical. Attempts to isolate terephthalic acid from oxidation products of the compound were unsuccessful. Eventually, the compound was shown by *X*-ray analysis to be the cyclic dimer, *tricyclo*[8 : 2 : 2 : $2^{4:7}$]hexadeca-4 : 6 : 10 : 12(1) : 13 : 15-hexaene (I), or di-*p*-xylylene (Brown and Farthing, *Nature*, 1949, **164**, 915; see also Part II, *J.*, 1953, 3265).



(I)

The acetone-soluble fraction was shown to contain at least five fractions by chromatography on alumina. One compound, m. p. 82°, separated by fractional precipitation, was shown (mixed m. p.) to be the linear dimer of *p*-xylene, *viz.*, 4 : 4′-dimethyldibenzyl. As interest was largely centred on the polymer, no more work was done on the acetone-soluble fraction. It may have contained other polymers of the xylenes, such as di-*m*-xylylene or tri-*p*-xylylene which are being examined by Baker *et al.* (*J.*, 1945, 27; *Chem. and Ind.*, 1950, 77). When kept, the acetone-soluble fraction partly sublimed in the form of platy crystals, shown (mixed m. p.) to be 4 : 4′-dimethyldibenzyl. They provided single crystals for *X*-ray examination (Part III, *loc. cit.*). The compound was too soluble to allow the easy growth of suitable crystals from solution.

Authentic samples of 4 : 4′-dimethyldibenzyl were made by the Wurtz condensation of 4-methylbenzyl chloride and by persulphate oxidation of *p*-xylene to see whether higher polymers could be formed by this method, but yields of linear dimer formed in the latter process were low and there was an abundance of oxidation products which were not examined. The former preparation provided a close analogy to the Wurtz condensation of *p*-xylylene dichloride (Part III).

## Experimental

*Preparation of Intermediates.*—*p*-Xylene (setting point 13·1°, 99·6% pure) was purified by filtration, drying ($CaCl_2$), boiling over sodium for 2 hr., and then distillation from the same sodium. It was then stored over " Drierite " (anhydrous $CaSO_4$) until used.

p-*Xylylene dichloride.* Equal weights of *p*-xylene and carbon tetrachloride were placed in a flask fitted with a gas lead and two double-surface reflux condensers in series with a calcium chloride tube and illuminated with a 100-w lamp. A trace of phosphoric oxide was added. Dry chlorine was passed into initially cold *p*-xylene, the flask being heated with a free flame when the heat of reaction was not sufficient to keep the solution gently boiling. Reaction was continued until the mixture solidified completely on standing overnight (approx. 30 hr.' chlorination for 1000 g. of *p*-xylene). This gave appreciable amounts of *p*-methylbenzyl chloride, but reduced the yield of trichloro-derivatives. The reaction mixture was fractionated at 12 mm. with a 6″ × 0·75″ column packed with glass helices, lagged and electrically heated. The first fraction, b. p. 50—95°/11 mm., was liquid, the second, b. p. 98—118°/10 mm., was a mixture of liquid and solid and was rejected, and finally *p*-xylylene dichloride came over at 135°/12 mm. (m. p. 90°). It was recrystallised from xylene, to yield free-flowing crystals, m. p. 98°, not raised by further recrystallisation. The crude product, m. p. 90°, was used for preparation of *p*-xylylene dicyanide. Both the crude and the pure product were mildly dermatitic and lachrymatory.

4-*Methylbenzyl chloride.* The fraction of b. p. 50—95°/11 mm. (above) was redistilled through the same short column in presence of a trace of phosphoric oxide. The bulk passed over at 78°/11 mm. as a colourless liquid. It was stored over a trace of phosphoric oxide.

p-*Di*-2-*chloroethylbenzene.* This was prepared in the usual manner from *p*-xylylene dichloride, through the cyanide (Ruggli and Theilheimer, *Helv. Chim. Acta*, 1941, **24**, 899). The crude product did not crystallise so it was purified by distillation (b. p. 92°/0·25 mm.) and then had m. p. 44°. Attempts to convert *p*-di-2-hydroxyethylbenzene into the dichloride by use of thionyl chloride were unsuccessful.

2 : 7-*Dimethylanthracene.* This was prepared by Morgan and Coulson's method (*J.*, 1929, 2203). The crude tarry product was warmed with water and a little wetting agent (sulphated long-chain alcohol), filtered through sintered glass, and washed with a little cold acetone. This product (1 g.) and pure ethylene glycol (150 c.c.) were distilled. When 100 c.c. had been collected and cooled to room temperature the distillate was filtered and put back to distillation. Three further lots of 50 c.c. were similarly treated. The residue from the filtrations comprised pale cream-coloured plates (0·9 g., 90%), m. p. 235°. Two recrystallisations from acetone gave a solid of constant m. p., 239°. The crystals dissolved in concentrated sulphuric acid to give an intense yellow colour which was discharged on addition to water and became red with a trace of concentrated nitric acid.

2 : 3 : 6 : 7- *and* 1 : 4 : 5 : 8-*Tetramethylanthracene.* These were made by Hey's method (*J.*, 1935, 72; 1938, 1847). They were readily purified by co-distillation with ethylene glycol. Both compounds gave the same yellow colour with concentrated sulphuric acid as did the 2 : 7-dimethylanthracene.

4 : 4′-*Dimethyldibenzyl.* 4-Methylbenzyl chloride (70 g.) and sodium (23 g., 100% excess) in *p*-xylene (redistilled from sodium) were heated under reflux for 2 hr. with stirring. When cold, the mixture was added to ethanol (500 c.c.). Water was added to dissolve the solid, and the ethanol removed by distillation. The residue was diluted with water and extracted with benzene. The extract was dried, and benzene and *p*-xylene were removed *in vacuo*. On cooling, the residual 4 : 4′-dimethyldibenzyl crystallised; it had m. p. 82° from ethanol. No other products were detected. Similarly addition of 4-methylbenzyl chloride (141 g.) during 1 hr. to a boiling suspension of sodium (23 g.) in dioxan (pure, dry, 500 c.c.) gave only 4 : 4′-dimethyldibenzyl.

*Dimerisation of* p-*Xylene by Aqueous Potassium Persulphate* (cf. Moritz and Wolffenstein, *Ber.*, 1899, **32**, 432, 2531).—*p*-Xylene (21·2 g.), potassium persulphate (54 g.), and water (600

c.c.) were stirred at 60—70° for 5 hr. When cold, the mixture was extracted with benzene, and the benzene removed on the steam-bath. There was obtained an oil which partly crystallised. Only 4 : 4′-dimethyldibenzyl could be isolated; aldehydes were present, as shown by formation of 2 : 4-dinitrophenylhydrazones. In view of the by-products, this method did not appear suitable for polymerisation.

*Low-molecular-weight Substances in* lin-*Poly*-p-*xylylene formed by Pyrolysis.*—Several small samples of this *lin*-poly-*p*-xylylene were found to contain varying amounts of chloroform-soluble bodies. In general, polymer prepared with high rates of flow through the pyrolysis apparatus contained the greatest proportion. The following is a typical experiment. *lin*-Poly-*p*-xylylene (3·673 g.) was extracted with redistilled chloroform (150 c.c.) for 4 hr. The chloroform was evaporated to ~3 c.c., and the concentrate washed into a weighed dish with chloroform. Solvent was removed *in vacuo* at room temperature over concentrated sulphuric acid and paraffin wax. There remained 0·923 g. of yellow solid. The extract was made into a slurry with pure dry acetone (5 c.c.), and the bulk dissolved. The residue was collected and washed with a little acetone. The filtrate and washings were kept over concentrated sulphuric acid *in vacuo* until the solvent was removed. There was obtained 0·0247 g. of acetone-insoluble matter.

*Properties of the Acetone-soluble Fraction.*—The fraction was generally a yellow solid; one sample was a mixture of oil and solid. It had the characteristic odour of 4 : 4′-dimethyldibenzyl. In all samples the solid started to melt below 55°, but never had a sharp m. p. It was chromatographed in benzene down a ½″ × 8″ column of alumina type O and developed with light petroleum (b. p. 60—80°). Examination in ultra-violet and visible light showed the following zones, starting from the top, purple (u.v.), brown (visible), yellow (visible), purple (u.v.), yellow (u.v.), and then a large purple (u.v.) zone. On storage, small amounts of sublimate were formed. One sample, in a shallow covered dish, yielded pale yellow plates and after 6 months these were scraped off. They were 4 : 4′-dimethyldibenzyl, shown by m. p. and mixed m. p. 82° (hot-stage microscope) to be identical with the sample prepared as above. The *X*-ray diffraction pattern of the powdered crystals was identical with that of the earlier sample. 4 : 4′-Dimethyldibenzyl was very soluble in all the common organic solvents, and good crystals for *X*-ray analysis could not be grown from solution. The sublimate gave suitable single crystals for an *X*-ray examination (see Part III, *loc. cit.*). The acetone-soluble fraction was fractionally precipitated from ethanol solution by water. A trace of a white solid, m. p. 100—120°, was isolated first, and from the later fractions, after recrystallisation from methanol, there was obtained 4 : 4′-dimethyldibenzyl, m. p. and mixed m. p. 82°. There were also traces of a solid more soluble than 4 : 4′-dimethyldibenzyl.

*Properties of the Acetone-insoluble Fraction.*—The crude product was obviously crystalline, melting range 248—280° (slight decomp.). It could be recrystallised from glacial acetic acid, anhydrous *NN*-dimethylformamide, and pyridine. After three recrystallisations from the last, it had m. p. 285°, unchanged by a further crystallisation from glacial acetic acid (Found: C, 92·1; H, 7·8. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%). The *substance* became red in concentrated sulphuric acid but did not dissolve. Attempts to oxidise it failed. Heating 4 : 4′-dimethyldibenzyl with sulphur at 200° for 12 hr. gave no di-*p*-xylylene, the product being a mixture of sulphur and a black resin. Another attempted synthesis, by the Wurtz condensation of *p*-xylylene dichloride at high dilution, is described in Part III (*loc cit.*).

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# 648. lin-*Poly*-p-*xylylene. Part II.* The Crystal Structure of Di*-p-*xylylene.*

By C. J. Brown.

One of the crystalline substances extracted from the polymer obtained by pyrolysis of *p*-xylene has been shown, solely by *X*-ray diffraction methods, to be a new compound, di-*p*-xylylene. A complete structure determination has been carried out, and it is found that the benzene rings are not flat; the two substituted carbon atoms in the *para*-positions are each displaced by 0·133 Å from the plane of the other four. The planes of these carbon atoms in a single molecule lie 3·09 Å apart. Bond lengths are all of normal values, the aromatic C–C distances being 1·39 and 1·40 Å, and the aliphatic 1·54 and 1·55 Å.

As described in Part I,* the products formed during the pyrolysis of *p*-xylene were largely polymeric, but extraction of some of these samples with chloroform (Soxhlet) yielded a mixture of crystalline compounds of comparatively low molecular weight. The major constituent was readily identified as 4 : 4′-dimethyldibenzyl, but one, insoluble in acetone, was unrecognised. A portion of the latter sample was recrystallised from pyridine, yielding tetragonal prisms which melted sharply at 285°.

The unit-cell dimensions of these crystals, which were obtained by measuring the layer-line spacings on *X*-ray rotation photographs, were $a = 7{\cdot}82$ and $c = 9{\cdot}33$ Å. The density of the crystals, as observed by flotation in sodium iodide solution, was 1·23, and hence the weight per unit cell was calculated to be *ca.* 420. Microanalysis gave a C : H ratio of 1 : 1, and since no other atoms were present, it seemed probable that the unit cell contained 32C + 32H, with weight of 416. A molecular-weight determination in the mass spectrometer gave the principal peak at 208, whence it appeared that the unit cell contained two molecules of $C_{16}H_{16}$.

All *X*-ray reflexions were present except those from planes $\{0kl\}$ with $(k + l)$ odd, indicating one glide plane in the tetragonal lattice. The space-group could therefore have been $P\bar{4}n2$ ($D_{2d}^{8}$), $P4_2nm$ ($C_{4v}^{4}$), or $P4_2/m.nm$ ($D_{4h}^{14}$). The first two of these are polar, and the third is centro-symmetrical; the choice could ideally have been made by a pyro- or piezo-electric test, but at the time there was scarcely sufficient specimen available. It was found in the course of the refinement of the structure that the space-group of highest symmetry $P4_2/m.nm$ ($D_{4h}^{14}$) was the correct one.

Apart from the information that the unit cell contained two molecules of a hydrocarbon derived from *p*-xylene of probable formula $C_{16}H_{16}$, nothing was known about the constitution of the substance at this stage. Since it was chemically reasonable that the substance should be 2 : 6- or 2 : 7-dimethylanthracene or 3 : 6-dimethylphenanthrene, samples of these compounds were examined by *X*-ray powder photography but their diffraction patterns were different from that of the new substance $C_{16}H_{16}$.

A complete set of *X*-ray intensity data was then obtained in the usual way, and attempts were made to fit a structure to them. The difficulty was to find a reasonable molecule $C_{16}H_{16}$ which would fit into the unit cell without overlapping its neighbours. Furthermore, the molecule must have the requisite symmetry. Fused-ring compounds were generally too bulky. It was evident that the molecule had to be fairly compact, and consideration was given to those of approximately spherical shape. When no further suitable trial structures could be suggested it was decided to compute a three-dimensional Patterson synthesis for a limited region around the origin, and as a preliminary to this, a two-dimensional Patterson synthesis was computed, using $F^2\{hk0\}$ terms only.

The result of this is shown in Fig. 1. There is a very pronounced peak *P* on the diagonal of this vector map at about 3 Å from the origin. This indicated that the majority of inter-atomic vectors superpose on this peak; the interpretation is that the peak would be accounted for by placing two benzene rings parallel to each other in planes 3 Å apart. A

* Part I, preceding paper.

model was made up on this basis, and with the substituent methyl groups placed appropriately at 1·5 Å from each other; good agreement between calculated and experimental structure amplitudes was at once obtained. This led to the characterisation of the compound as di-*p*-xylylene as already reported briefly (Brown and Farthing, *Nature*, 1949, **164**, 915), and further Patterson syntheses were rendered unnecessary.

No previous mention of di-*p*-xylylene could be found. Since this work was completed, its preparation has been achieved by other workers (Cram and Steinberg, *J. Amer. Chem. Soc.*, 1951, **73**, 5691). Attention was drawn to the analogous di-*o*-xylylene (Baker, Banks, Lyon, and Mann, *J.*, 1945, 27), on which some *X*-ray work was proposed, but apparently never commenced, and to di-*m*-xylylene, originally prepared by Pellegrin (*Rec. Trav. chim.*, 1899, **18**, 458) and more recently confirmed by Baker, McOmie, and Norman (*Chem. and Ind.*, 1950, **77**; *J.*, 1951, 1114). The complete structure determination of di-*m*-xylylene

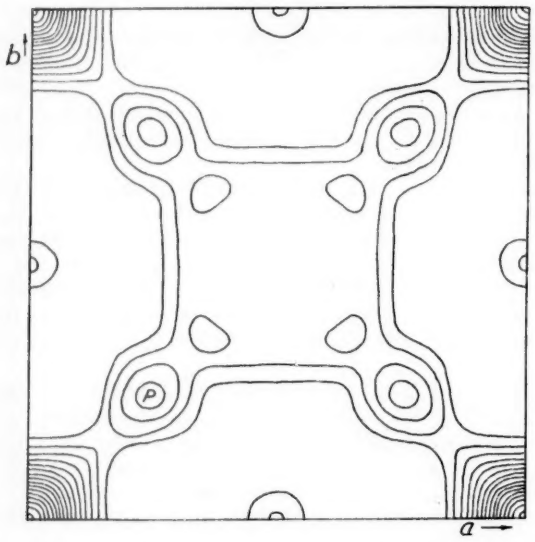



FIG. 1. *Patterson vector map obtained by projection along* c *axis.*

by *X*-ray diffraction, using crystals kindly supplied by Baker, has now been completed (Brown, *J.*, 1953, 3278).

As di-*p*-xylylene would generally be regarded as a stereochemically impossible compound owing to the distortions necessary, a complete quantitative *X*-ray study was made, so as to determine the bond lengths and inter-bond angles. After the two-dimensional Patterson synthesis, refinement was carried out first by means of two-dimensional Fourier syntheses, projecting along *c* and then along *a*. The *c* projections were not very fruitful as they gave only *x* co-ordinates, and the resolution of the atoms was poor because only 40 {*hk*0} reflexions were observed. The *a* projections gave both *x* and *z* co-ordinates, but the resolution was still poor as only 45 {0*kl*} reflexions were observed. It thus became necessary to employ three-dimensional syntheses.

At this stage, no choice had been made between the three permissible space-groups. That of the lowest symmetry, $P\bar{4}n2$, was chosen for structure amplitude calculations, and the whole set of F{*hkl*} computed. The sum of the *B* components ($F^2 = A^2 + B^2$) of the terms used in the synthesis was almost zero, with the result that the non-equivalent atoms moved from their original positions to positions which they would occupy in the space-group $P4_2/m.nm$. This led to adoption of this centrosymmetrical space-group, and as nothing emerged in the subsequent refinement to throw doubt on the choice, this space-group may be regarded as established. In this space-group, which has a 16-fold general position, out of the 32 carbon atoms in the unit cell, 16 lie in a general position, all related

by symmetry elements, and the remaining 16 in two groups of 8 in 8-fold special positions, thus (the nomenclature being that of the International Tables for *X*-Ray Crystallography):

16 *k*: $x, y, z$; $\bar{x}, \bar{y}, z$; $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}+z$; $x, y, \bar{z}$; $\bar{x}, \bar{y}, \bar{z}$; $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}-z$; $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$; $y, x, z$; $\bar{y}, \bar{x}, z$; $\frac{1}{2}+y, \frac{1}{2}-x, \frac{1}{2}+z$; $\frac{1}{2}-y, \frac{1}{2}+x, \frac{1}{2}+z$; $y, x, \bar{z}$; $\bar{y}, \bar{x}, \bar{z}$; $\frac{1}{2}+y, \frac{1}{2}-x, \frac{1}{2}-z$; $\frac{1}{2}-y, \frac{1}{2}+x, \frac{1}{2}-z$.

8 *j*: $x, x, z$; $\bar{x}, \bar{x}, z$; $\frac{1}{2}+x, \frac{1}{2}-x, \frac{1}{2}+z$; $\frac{1}{2}-x, \frac{1}{2}+x, \frac{1}{2}+z$; $x, x, \bar{z}$; $\bar{x}, \bar{x}, \bar{z}$; $\frac{1}{2}+x, \frac{1}{2}-x, \frac{1}{2}-z$; $\frac{1}{2}-x, \frac{1}{2}+x, \frac{1}{2}-z$.

There are therefore seven parameters to be determined, $x$, $y$, and $z$ for the carbon atoms in the general position, and $x$ and $z$ for each of the two carbon atoms in special positions. As shown in Fig. 2, in any given molecule of di-*p*-xylylene, only three of the sixteen carbon atoms are crystallographically different. This is due to the three mirror reflexion planes at right angles in the molecule meeting in a centre of symmetry, which coincides with a centre of symmetry in the unit cell.

Two sets of three-dimensional Fourier syntheses were computed successively in order to determine the seven parameters. After the first, it was observed that carbon atom 2 was displaced from the position it should occupy if the benzene ring were rigidly planar. It was restored to this position in the plane before the structure amplitudes were re-calculated, but the second synthesis confirmed the displacement. The final atomic co-ordinates are:

| | *x* | *y* | *z* |
|---|---|---|---|
| Carbon 1 | 0·070 | 0·070 | 0·030 |
| Carbon 2 | 0·128 | 0·128 | 0·150 |
| Carbon 3 | 0·248 | 0·032 | 0·075 |

The corresponding composite electron-density map is shown in Fig. 3. If the benzene ring were rigidly planar, the $x$ and $y$ co-ordinates of carbon atom 2 would be each 0·140 instead of 0·128, so the displacement of carbon 2 from the plane of the other four atoms in the ring is given by $0{\cdot}012a\sqrt{2} = 0{\cdot}133$ Å. That the displacement is genuine is shown by the results of the two successive three-dimensional syntheses, and there is therefore evidence of a slightly bent, boat-shaped benzene ring. The bending is presumably occasioned by the necessity of reducing the strain in the system; this can be done without altering the bond-lengths or angles very greatly from their standard values, as shown in Table 1. Two views of the molecule at right angles to each other are shown in Fig. 4.

TABLE 1.

(a) *Bond lengths* (Å):
$C_1$–$C_1'$ (aliphatic) = 1·55, $C_1$–$C_2$ (aliphatic) = 1·54, $C_2$–$C_3$ (aromatic) = 1·39, $C_3$–$C_3'$ (aromatic) = 1·40.

(b) *Inter-bond angles*:
$C_2\widehat{C_1}C_1' = 114°\ 37'$, $C_3\widehat{C_2}C_3' = 118°\ 36'$, $C_1\widehat{C_2}C_3 = 119°\ 55'$, $C_2\widehat{C_3}C_3' = 120°\ 14'$.

(c) *Intra-molecular distances* (Å) *between non-bonded atoms*:
$C_2$–$C_2' = 2{\cdot}83$, $C_3$–$C_3' = 3{\cdot}09$.

(d) *Inter-molecular distances* (Å):
$C_1$–$C_1'$ (along *c* axis) = 3·73, $C_1$–$C_3$ (along 111 approx.) = 4·06.

After the positions of the carbon atoms had been determined, an attempt was made to locate the hydrogen atoms by computing three-dimensional difference syntheses, using F(exp.) −F(calc.) as coefficients. The result of this was that, although there were regions of positive electron density in places where hydrogen atoms would be expected to occur, there were no very clearly defined maxima in these regions. Theoretical positions were therefore chosen for the hydrogen atoms at distances of 1·08 Å from the carbon atoms to which they are attached, as follows:

| | *x* | *y* | *z* |
|---|---|---|---|
| Hydrogen 1 (attached to Carbon 1) | 0·210 | 0·020 | 0·362 |
| Hydrogen 2 (attached to Carbon 3) | 0·332 | 0·948 | 0·133 |

The co-ordinates of the other hydrogen atom attached to carbon 1 may, of course, be derived from those of hydrogen 1 by the usual symmetry operation of the space-group,

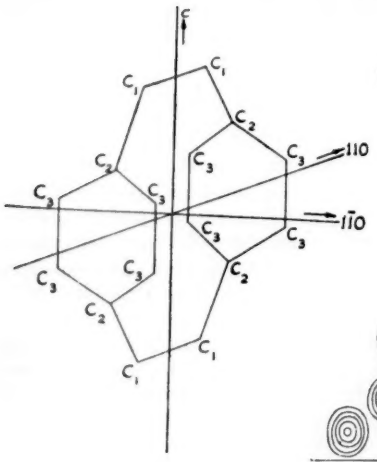



FIG. 2. *Molecule of di-p-xylylene showing location with respect to three axes and three mirror reflexion planes at right angles.*

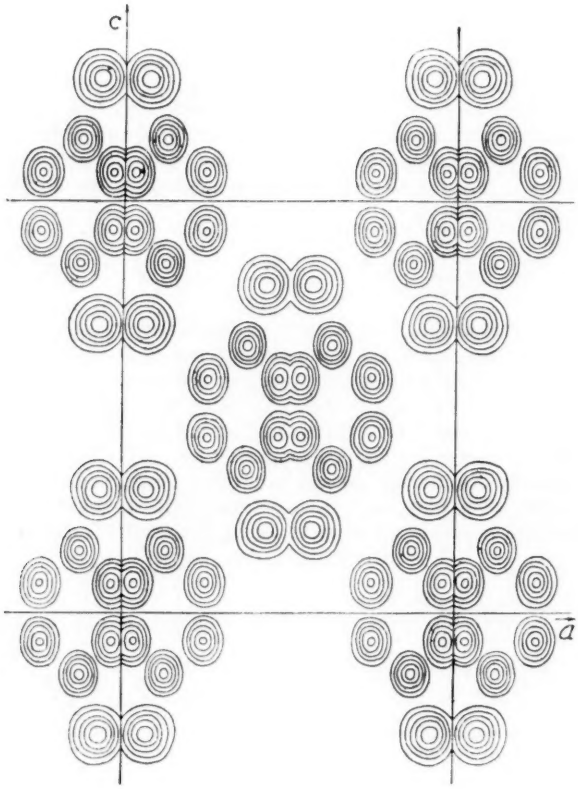
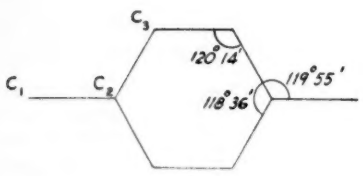
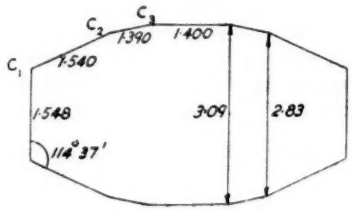



FIG. 3. *Composite electron-density map resulting from sections of a three-dimensional Fourier synthesis at appropriate values of y. Contours are at intervals of* 1 eÅ$^{-3}$.

FIG. 4. *Two views of the molecule of di-p-xylylene at right angles, showing dimensions and distortion from planarity.*



*i.e.*, reflexion across (110). These hydrogen atomic co-ordinates were used in calculating the structure amplitudes listed in Table 2.

TABLE 2.

| *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 000 | — | 224 | 341 | 9·8 | + 8·2 | 363 | 1·3 | − 0·6 | 146 | 1·4 | + 2·1 |
| 020 | 16 | +16 | 351 | 3·4 | + 4·0 | 383 | 1·5 | + 0·6 | 156 | 1·4 | − 1·5 |
| 040 | 8·2 | + 7·8 | 361 | 2·6 | − 2·2 | 443 | 4·1 | − 3·3 | 166 | 3·0 | + 2·5 |
| 060 | 7·0 | − 5·9 | 371 | 5·5 | + 2·8 | 453 | 2·4 | − 1·3 | 176 | 0·7 | + 0·3 |
| 080 | 4·1 | + 1·6 | 441 | 2·6 | + 2·2 | 463 | 1·3 | − 0·7 | 186 | 0·8 | + 0·4 |
| 110 | 38 | +46 | 451 | 4·0 | + 3·5 | 473 | 2·2 | + 1·3 | 226 | 4·8 | + 8·8 |
| 120 | 34 | −36 | 551 | 7·1 | − 5·0 | 573 | 1·5 | + 0·5 | 236 | 4·2 | − 5·1 |
| 130 | 7·0 | − 4·7 | 561 | 2·3 | − 1·2 | 583 | 1·4 | + 0·6 | 246 | 1·0 | − 0·7 |
| 140 | 12 | −11 | 661 | 1·7 | − 0·8 | 663 | 2·5 | + 0·7 | 256 | 2·2 | + 2·1 |
| 150 | 6·8 | − 6·3 | 002 | 1·5 | − 1·1 | 004 | 16 | −17 | 266 | 2·0 | + 1·6 |
| 160 | 2·1 | − 1·8 | 022 | 10 | −12 | 024 | 1·8 | + 1·2 | 286 | 1·2 | − 0·6 |
| 180 | 2·4 | − 1·5 | 042 | 16 | +15 | 044 | 1·8 | + 1·5 | 336 | 1·3 | + 1·9 |
| 190 | 0·4 | − 0·2 | 082 | 1·7 | + 1·5 | 084 | 2·0 | − 1·7 | 346 | 2·3 | − 2·4 |
| 220 | 38 | −38 | 112 | 18 | −22 | 114 | 1·8 | − 1·9 | 017 | 2·1 | + 2·0 |
| 230 | 18 | −17 | 122 | 4·0 | + 5·0 | 124 | 6·0 | + 6·9 | 037 | 3·4 | − 4·5 |
| 250 | 2·2 | − 2·3 | 132 | 0·6 | − 0·6 | 134 | 3·8 | + 4·2 | 057 | 3·2 | − 3·3 |
| 260 | 7·6 | − 7·0 | 142 | 1·2 | − 1·0 | 164 | 1·0 | − 1·1 | 117 | 1·0 | − 1·1 |
| 270 | 3·1 | + 2·4 | 152 | 3·3 | + 4·1 | 174 | 1·0 | − 1·3 | 127 | 4·0 | + 5·6 |
| 280 | 2·0 | + 0·5 | 162 | 3·0 | − 2·4 | 184 | 0·5 | + 0·4 | 137 | 1·4 | − 1·5 |
| 290 | 1·6 | − 0·5 | 172 | 1·0 | + 1·3 | 194 | 0·5 | − 0·3 | 147 | 4·1 | − 4·4 |
| 330 | 4·0 | + 5·4 | 182 | 1·5 | − 1·0 | 224 | 6·2 | + 7·1 | 157 | 2·6 | + 2·5 |
| 340 | 1·8 | − 1·1 | 222 | 20 | −23 | 234 | 2·2 | + 1·4 | 167 | 0·9 | + 0·5 |
| 350 | 2·0 | + 1·9 | 232 | 11 | +12 | 254 | 2·0 | − 2·8 | 177 | 1·3 | + 0·6 |
| 360 | 5·4 | + 3·7 | 242 | 3·0 | + 1·8 | 274 | 1·3 | − 1·0 | 227 | 2·8 | − 4·9 |
| 370 | 1·8 | − 1·9 | 262 | 2·4 | − 1·0 | 334 | 2·3 | − 2·5 | 237 | 2·2 | + 3·0 |
| 380 | 2·0 | + 1·6 | 282 | 2·0 | + 1·4 | 344 | 3·0 | − 2·6 | 267 | 1·2 | + 0·9 |
| 440 | 14 | +13 | 342 | 6·8 | + 7·8 | 354 | 2·0 | − 1·6 | 337 | 5·2 | − 5·7 |
| 450 | 4·5 | − 6·1 | 362 | 2·2 | + 2·1 | 364 | 2·2 | − 1·9 | 008 | 4·5 | − 6·6 |
| 460 | 2·0 | − 0·7 | 382 | 1·6 | + 0·4 | 444 | 3·9 | − 4·1 | 028 | 1·4 | − 1·4 |
| 470 | 2·2 | + 1·0 | 442 | 3·2 | + 2·4 | 564 | 2·4 | + 1·1 | 048 | 2·5 | − 2·7 |
| 550 | 2·0 | + 2·2 | 462 | 2·0 | − 0·7 | 015 | 12 | −16 | 068 | 1·4 | + 1·2 |
| 560 | 5·2 | − 3·9 | 552 | 1·4 | − 1·0 | 035 | 4·2 | − 5·5 | 118 | 1·3 | − 1·7 |
| 580 | 1·3 | − 0·3 | 013 | 7·0 | + 7·0 | 075 | 1·2 | + 0·8 | 128 | 0·9 | + 0·9 |
| 660 | 1·7 | + 0·1 | 033 | 9·3 | +10·0 | 115 | 2·7 | + 4·0 | 138 | 1·0 | − 0·8 |
| 670 | 1·4 | + 0·2 | 053 | 2·7 | + 2·3 | 125 | 1·0 | + 0·8 | 148 | 1·6 | + 1·7 |
| 011 | 37 | +35 | 073 | 3·0 | − 2·9 | 135 | 2·6 | + 4·4 | 158 | 0·7 | + 0·3 |
| 031 | 7·3 | + 5·9 | 093 | 1·2 | − 0·7 | 145 | 2·3 | − 2·6 | 168 | 1·2 | + 1·0 |
| 051 | 1·0 | + 1·3 | 113 | 3·1 | + 3·0 | 155 | 3·4 | + 3·8 | 178 | 0·5 | + 0·5 |
| 071 | 2·2 | + 3·3 | 123 | 4·4 | + 5·6 | 165 | 3·1 | + 3·7 | 228 | 1·9 | + 2·9 |
| 091 | 0·6 | + 0·4 | 133 | 0·8 | + 0·7 | 175 | 1·2 | + 0·6 | 258 | 1·5 | + 1·3 |
| 111 | 14 | −17 | 143 | 5·8 | + 5·4 | 225 | 3·8 | + 4·3 | 268 | 2·0 | + 1·2 |
| 121 | 25 | −24 | 153 | 5·1 | − 5·3 | 235 | 2·4 | + 2·4 | 019 | 2·4 | − 2·3 |
| 131 | 6·1 | − 6·5 | 163 | 2·6 | − 3·1 | 245 | 2·3 | + 3·4 | 059 | 0·8 | + 0·3 |
| 141 | 5·8 | + 5·8 | 173 | 2·3 | − 1·0 | 255 | 1·7 | − 2·8 | 119 | 1·0 | + 1·1 |
| 151 | 4·2 | − 3·6 | 183 | 1·8 | − 1·5 | 345 | 1·0 | − 1·7 | 139 | 0·9 | + 0·9 |
| 161 | 3·7 | − 4·6 | 193 | 0·5 | + 0·4 | 355 | 1·3 | + 1·5 | 169 | 0·5 | + 0·3 |
| 171 | 1·2 | − 0·5 | 223 | 6·8 | + 5·9 | 365 | 1·8 | + 1·3 | 229 | 1·3 | + 1·3 |
| 181 | 3·8 | + 2·3 | 233 | 1·7 | − 2·1 | 006 | 2·2 | − 4·5 | 269 | 0·6 | − 0·2 |
| 191 | 2·0 | − 1·2 | 243 | 3·7 | − 4·7 | 126 | 1·4 | + 1·5 | 0.2.10 | 0·9 | + 0·8 |
| 221 | 8·1 | − 8·2 | 253 | 2·4 | − 2·0 | 046 | 8·2 | − 8·7 | 0.4.10 | 0·9 | + 0·6 |
| 231 | 8·2 | − 8·3 | 263 | 4·4 | − 3·8 | 066 | 1·1 | + 0·8 | 1.1.10 | 0·8 | + 0·5 |
| 241 | 1·8 | + 2·4 | 273 | 1·4 | − 1·2 | 116 | 3·6 | + 4·0 | 1.2.10 | 0·7 | + 0·5 |
| 251 | 2·3 | − 3·2 | 343 | 4·2 | − 3·5 | 126 | 1·4 | − 1·6 | 1.3.10 | 1·0 | + 0·8 |
| 261 | 3·0 | + 2·2 | 353 | 3·8 | − 4·3 | 136 | 1·2 | − 1·6 | 2.5.10 | 1·4 | − 0·6 |
| 331 | 10·7 | +10·7 | | | | | | | | | |

## EXPERIMENTAL

Crystals of di-*p*-xylylene grown from pyridine were tetragonal prisms {110} exhibiting rather imperfect {111} pyramids. The cross-section of some specimens resembled a cross, but the suggested presence of multiple twins of lower symmetry was never confirmed. A section cut parallel to (001) gave an excellent uniaxial interference figure in convergent polarized light. The tetragonal system was further confirmed by the perfect identity of oscillation photographs about *c* taken 90° apart.

*X*-Ray intensity data were obtained from Weissenberg moving-film photographs of the zero and three layers about *a*, and the zero and four layers about *c*. Owing to a relatively high temperature factor which caused the reflexions to fall off to zero before $\theta = 90°$ with

Cu-$K\alpha$ radiation, all the diffraction data obtainable at room temperature were recorded on these photographs, totalling in all about 270 reflexions. The multiple-film technique was employed, and the intensities estimated visually with the aid of a time-exposure calibrated film strip. The usual corrections were applied for polarization and angular velocity.

*Structure Amplitude Calculations.*—In order to obtain agreement with the experimental F's, it was necessary to apply a rather large value of $B$ ($8{\cdot}0 \times 10^{-16}$ Å$^2$) to the atomic scattering factors used in calculating the structure amplitudes. This is an unusually large temperature factor for a crystal which melts as high as 285°. As about 94% of the F's had values less than 10, one place of decimals was used for these small terms in both the experimental and calculated structure amplitudes, which are listed in Table 2. There are about 50 planes with small unobserved intensities within the range observable with Cu-$K\alpha$ $X$-rays, and these have been omitted from the Table. The usual residual $R = \dfrac{\Sigma|\mathrm{F(exp.)}| - |\mathrm{F(calc.)}|}{\Sigma \mathrm{F(exp.)}}$ amounts to 0·18 when the hydrogen atoms are neglected, and 0·14 when they are included, summed over all values of ($hkl$).

The author thanks Mr. A. C. Farthing for extracting and purifying the samples used from preparations of polymer by Messrs. Gill and Lord.

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## 649. lin-*Poly*-p-*xylylene. Part III.* Preparation by the Wurtz Reaction, and Investigation of Structure.*

By C. J. Brown and A. C. Farthing.

*lin*-Poly-*p*-xylylene is prepared from *p*-xylylene dichloride by the Wurtz reaction and is shown by $X$-ray methods to be identical with the polymer prepared by pyrolysis of *p*-xylene. Oxidative degradation shows the polymer to be linear; it is dimorphic, both forms, α and β, being characterised by $X$-ray powder patterns, and they can be separated by fractionation methods. The α- is converted into the β-form by heat, but the transformation could not be reversed. $X$-Ray evidence indicates that the α-form has a stepped structure whilst the β-form is planar.

The production of a polymeric substance during the pyrolysis of *p*-xylene at low pressures by Szwarc (*J. Chem. Phys.*, 1948, **16**, 128) gave rise to the question of its structure. It was decided to examine the preparation of similar material by a classical organic synthetic method which might be expected to afford greater control, and then to compare the product, by $X$-ray diffraction, with polymer formed by pyrolysis. Wurtz condensation of *p*-xylylene dichloride did not occur at all in benzene, and only very slowly in toluene to give an amorphous polymer. *p*-Xylene was thought to be a suitable medium because if it took part in the Wurtz reaction by trans-metallation or radical interchange then the product would be of unchanged structure. The Wurtz reaction took place rapidly in *p*-xylene, yielding a solid product which on purification generally had a diffraction pattern identical with that of polymer prepared by the pyrolysis method. When dioxan was used as solvent reaction was extremely rapid and violent.

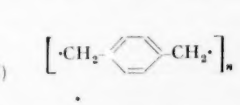
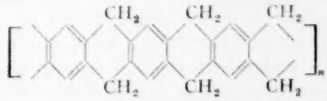
Friedel–Crafts condensation of phenethyl chloride gave an amorphous polymer, no doubt owing to reaction at both *o*- and *p*-positions on the ring, whereas formation of *lin*-poly-*p*-xylylene requires reaction exclusively at the *p*-position.

Oxidation of the pyrolysis polymer yielded terephthalic acid along with only 0·1% of *iso*phthalic acid. This indicated primarily a structure (I), the traces of *iso*phthalic acid arising from *m*-xylylene units in the chain, which were probably formed by isomerisation of the *p*-xylene in the pyrolysis apparatus. An alternative structure (II), based on the known pyrolysis of *p*-xylene to dimethylanthracenes (Part I), is ruled out.

Wurtz condensation of 4-methylbenzyl chloride yielded only 4 : 4′-dimethyldibenzyl,

* Part II, preceding paper.

and by analogy it is likely that *p*-xylylene dichloride would react similarly to give poly-*p*-xylylene. It has been shown (Szwarc, *Discuss. Faraday Soc.*, **1947**, **2**, 39) that the bond

(I)   (II)

between the aliphatic carbon atoms in dibenzyl is stabilised by resonance and this stabilisation may occur in the polymer.

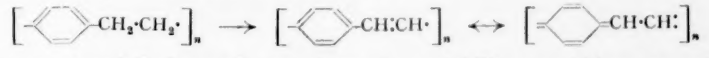
The polymerisation in the pyrolysis apparatus is a combination of free radicals, and the literature shows three cases of dimerisation of *p*-xylene, probably by a homolytic mechanism. Aqueous potassium persulphate oxidises *p*-xylene to 4 : 4′-dimethyldibenzyl, (Part I); the decomposition of phenyl azide in *p*-xylene gives the same compound (Bertho, *Ber.*, **1924**, **57**, **1138**); and when a solution of benzophenone in *p*-xylene is exposed to sunlight (Paterns and Chieffi, *Gazzetta*, **1909**, **39**, II, 428) 4 : 4′-dimethyldibenzyl is among the products. By analogy, the higher polymer formed from the free radicals would be expected to have the same structure as the dimer formed from the same radicals. This argument is supported by the occurrence of both the linear dimer (4 : 4′-dimethyldibenzyl) and the cyclic dimer (di-*p*-xylylene) in the pyrolysis polymer.

Although polymer prepared by both the Wurtz and the pyrolysis method gave similar *X*-ray diffraction patterns, it was observed that the relative intensities of certain rings on the powder photographs were different. By adjusting the conditions of preparation of the polymer the ratio of these intensities could be varied. The evidence pointed to the presence of two components, and these were separated by making use of their differential solubilities. For example, extraction of the Wurtz polymer with chloroform (Soxhlet) removed only the α-modification; and when the pyrolysis polymer was dissolved in boiling benzyl benzoate, and cooled, the portion separating first was the β-modification.

The α- was transformed into the β-form by heating above the melting point, but numerous attempts to carry out the reverse process were unsuccessful.

Probable structures of the two modifications of the polymer were suggested by comparing their *X*-ray powder photographs with the powder photographs and known structures of corresponding monomeric substances. It is not generally possible to derive an unambiguous crystal structure from a powder photograph of a substance of low symmetry, but in the case of the two forms of *lin*-poly-*p*-xylylene there are two series of closely related substances whose structures are already known, and these were of great assistance in deducing the probable structures of the polymers.

The unit-cell dimensions suggested for the α- and the β-form of the polymer account for all the reflexions observed in their powder photographs as shown in Tables 2 and 4. The configuration of the α-form of the polymer was taken to be similar to that of the molecule of 4 : 4′-dimethyldibenzyl; the benzene rings lie parallel to each other in the same molecule but are not co-planar; they are arranged stepwise. In the β-form of the polymer, the benzene rings are both parallel and co-planar as in the molecule of diphenyl; it follows that the $\cdot CH_2 \cdot CH_2 \cdot$ grouping also lies in the plane of the rings whereas in the α-modification it forms the step. It is not impossible that the β-form may be quinonoid as has been suggested by Goldfinger (*J. Polymer Sci.*, 1949, **4**, 93) for polyphenylene, but if this is so, two hydrogen atoms would be lost from each $\cdot CH_2 \cdot CH_2 \cdot$ grouping, and this might account for the irreversibility of the transition from α to β :



This difference, especially in a polymer of very low solubility, would be extremely difficult to detect.

## Experimental

*Preparation of Polymer by the Action of Sodium on* p-*Xylylene Dichloride*.—Apparatus for Wurtz reactions and for immediate manipulation of reagents was dried by baking at 100° for several hours. *p*-Xylylene dichloride was dried (over $CaCl_2$) for several days. Solvents were

dried over sodium and distilled directly into the apparatus. Exits from the apparatus were protected by tubes containing "Drierite" ($CaSO_4$).

(a) *Preparation in* p-*xylene.* In a 1-l. flask fitted with a rapid stirrer and reflux condenser *p*-xylylene dichloride (30 g.), *p*-xylene (100 c.c.), and sodium (10 g., an excess of 2·1 g.) were heated carefully. When the b. p. was reached a spontaneous reaction occurred and subsided in 1 min. The precipitate formed was deep purple. The mixture was then heated under reflux for a further 1·5 hr. The solid was filtered off, washed with ethanol, and stirred for 2 hr. with water, during which the blue mixture became pale cream in colour. It was then stirred with water for a week (the water being changed daily), filtered, washed with ethanol, and dried *in vacuo* ($CaCl_2$). The product (sample 5, 16·45 g.; 93·5%) was more soluble than sample 4 (prepared in toluene); it swelled and partly dissolved in hot naphthalene, ditolylmethane, and *m*-cresol. The solutions were not viscous. It was almost completely soluble in boiling benzyl benzoate and dibenzyl terephthalate, but "ghosts" of swollen particles were just visible (Found: C, 88·8; H, 7·45; Cl, 1·0; residue, 1·9%; C : H = 1). The *X*-ray photograph showed three rings of spacing 3·9, 4·4, and 5·3 Å, showing a moderate degree of crystallinity. The intensities of the 3·9 and 5·3 Å rings were greater than that of the 4·4 Å ring, and the photograph bore a marked resemblance to those of polymer obtained by pyrolysis of *p*-xylene. Reproductions of typical diffraction patterns are shown in the Plate.

(b) *Preparation in absence of solvent.* When sodium and excess of *p*-xylylene dichloride were warmed together in a test-tube, with suitable protection, a spontaneous reaction occurred after the dichloride had melted. A spongy solid formed round the sodium and swelled up the tube. When cold, the polymer was washed and dried as before. It was similar in appearance to the polymer sample 5, but not quite as soluble.

(c) *Further preparations of polymer.* The experimental procedure was similar to that adopted above. Some of the results are summarised in the Table.

| Polymer sample no. | *p*-Xylylene dichloride: charged (g.) | unreacted (g.) | Yield of polymer: (g.) | (%) | Na (g.) | Solvent (c.c.) | |
|---|---|---|---|---|---|---|---|
| 6 | 30 | 18 | 6·5 | 95 | 10 | *p*-Xylene | 250 |
| 10 | 30 | — | 2 | — | 10 | Ditolylmethane | 250 |
| 7 | 30 | 5 | 13 | 90 | 10 | *p*-Xylene | 164 |
| 8 | 30 | — | 8 | — | 10 | Dioxan | 250 |
| 9 | 10 | — | 2 | — | 4 | Dioxan | 250 |

Sample 6. The polymer had similar properties to sample 5. The *X*-ray photograph showed that the degree of crystallinity, judged by visual comparison, was slightly higher, and the three principal diffraction rings were roughly of equal intensity.

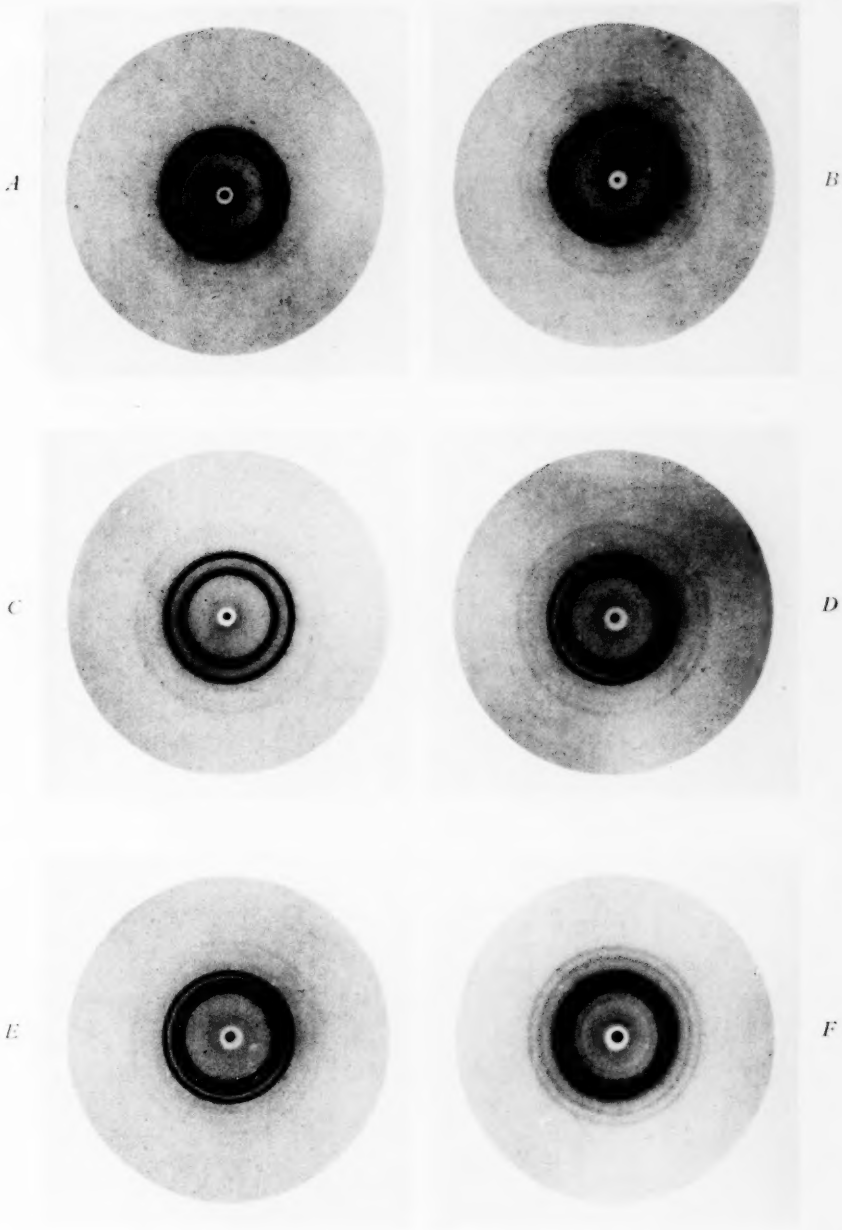
Sample 10. The solvent (mixed isomers from methylene dichloride and toluene) was not distilled directly in the reactor. Reaction was slow at 200°. After 10 min. at 220° the solution was black. The polymer was filtered off, and washed thoroughly with ethanol and benzene. It was swollen by hot naphthalene and acenaphthene, but remained generally insoluble. The *X*-ray photograph showed the sample to be mainly amorphous, but there was indication of three crystalline rings due to spacings of 3·9, 4·4, and 5·3 Å.

Sample 7. This was apparently identical with sample 6.

Sample 8. The Wurtz reaction in this case was very violent and material was ejected from the reactor. However, the residue in the flask was worked up in the usual manner. The polymer was almost pure white and was more powdery than the other preparations. It was the most soluble of the polymers prepared by the Wurtz reaction, but did not completely dissolve in hot naphthalene, acenaphthene, benzyl benzoate, or dibenzyl terephthalate; faint "ghosts" of swollen particles were just visible in the solution. The *X*-ray photograph showed the same three principal diffraction rings as the previous samples 4—7, but the relative intensities were markedly different. The middle of the three rings was considerably more intense than the other two. This gave the first hint about the composition of the polymer.

Sample 9. The sodium was added in 0·5-g. portions. In solubility it resembled sample 8, but the *X*-ray diffraction pattern was identical with that of samples 6 and 7.

Polymer samples 30 and 31. In a 3-l. flask were placed *p*-xylene (1475 c.c.) and sodium (10 g.). The *p*-xylene was gently boiled over an oil-bath. *p*-Xylylene dichloride (30 g.) was added in small portions during 4½ hr., and the mixture boiled for a further 4½ hr. The mixture was concentrated to *ca.* 200 c.c. and filtered hot. The residue was worked up in the usual way, to yield polymer sample 31, which resembled samples 5, 6, and 7 except that it was paler in colour. The *X*-ray photograph showed rings due to the usual spacings of 3·9, 4·4, and 5·3 Å,




X-*Ray diffraction patterns of* lin-*poly*-p-*xylylene*.

*A*, Pyrolysis polymer (sample **22**).
*B*, Wurtz polymer (sample **12**).
C, α-Form of polymer (sample **13**).
*D*, α + small amount of β (sample **14**).
*E*, α + β, approx. equal amounts (sample **15**).
*F*, β-Form of polymer (sample **29**).

[*To face p.* 3272.

but the middle ring was very weak. There was also a background of scattering due to amorphous material. The filtrate from the hot reaction mixture was concentrated on the steam-bath at the water-pump, to about 20 c.c. On cooling, a gummy precipitate appeared. This was washed with acetone and dried to give sample **30**. It melted at 120—150° to yield a viscous liquid. It was soluble in hot pyridine and was precipitated as a sludge on cooling. No di-*p*-xylylene could be detected. The *X*-ray photograph was well defined, showing the material to be of high crystallinity. It had rings corresponding to the three common spacings but there were also additional rings resembling those of 4 : 4′-dimethyldibenzyl.

*Self-condensation of Phenethyl Chloride*.—Phenethyl chloride, freshly distilled, was polymerised by anhydrous aluminium chloride after Sizido and Kato (*Chem. Abs.*, **1941**, **35**, 3246). The product was washed free from aluminium chloride and phenethyl chloride. On drying in air a hard brittle solid (sample **32**) remained. The *X*-ray photograph of sample **32** was that of amorphous material. Freshly distilled phenethyl bromide gave a similar product.

*Wurtz Condensation of* p-*Di-2-chloroethylbenzene*.—*p*-Di-2-chloroethylbenzene (4·85 g., Part I) and sodium (2 g., an excess) in *p*-xylene (47 c.c.) in a 250-c.c. 3-necked flask were used, the technique described above being followed. The reaction proceeded exactly as with *p*-xylylene dichloride. The blue-brown precipitate of polymer was similarly treated to produce 1·6 g. (50%) of pale yellow polymer (sample **33**). It was insoluble in all common organic solvents, but it was swollen readily by the solvents which swelled the *lin*-poly-*p*-xylylene prepared by the Wurtz reaction. It had a slightly lower m. p. than Wurtz *lin*-poly-*p*-xylylene. A comparison was made with sample **16** in an electrically heated capillary m. p. apparatus by use of a 550° mercury-in-glass thermometer which took two tubes and enabled comparison to be made. Results were not exactly reproducible, but poly-*p*-xylylene had the higher m. p., 420—430°, as against 395—415° for sample **33**. Sample **33** gave an *X*-ray diffraction pattern characteristic of amorphous material. The mother-liquors from the Wurtz reaction on evaporation to dryness in air and finally *in vacuo* gave a viscous orange-coloured resin (1·3 g., 40%) free from the odour of *p*-di-2-chloroethylbenzene.

*Wurtz Condensation of* p-*Dichlorobenzene*.—*p*-Dichlorobenzene (redistilled, 30 g.) and sodium (11 g., an excess) in *p*-xylene (350 c.c.) failed to react after prolonged boiling. In dioxan (100 c.c.) a smooth reaction occurred on boiling. As the reaction started, a cold-water bath was applied for a moment. The liquors became brown and a deep blue solid was precipitated. The mixture was left to cool, and methanol (800 c.c.) slowly added, causing a sludge to be formed. The mixture was stirred overnight, and the residue was collected and washed as usual, to yield a brown powder (sample **36**), m. p. 220° (cf. Goldfinger, *loc. cit.*, m. p. >300°), soluble in benzyl benzoate (Found: C, 82·55; H, 4·6; Cl, 10·65. Calc. for $[C_6H_4]_8Cl_2$: C, 84·8; H, 4·7; Cl, 10·5%). *X*-Ray examination showed sample **36** to be amorphous even after melting (sample **37**). The filtrate from the isolation of sample **36** from the reaction mixture was concentrated and yielded a series of fractions of varying solubility. The more soluble ones smelt of diphenyl. The least soluble fraction (sample **38**) was submitted to *X*-ray analysis and shown to be crystalline, but there was some amorphous background. The general appearance of the rings on the photograph was closely similar to that of the rings of β-*lin*-poly-*p*-xylylene, sample **21**.

*Investigation of the Structure of* lin-*Poly*-p-*xylylene*.—Polymer obtained by pyrolysis of *p*-xylene ("pyrolysis polymer") was completely soluble in boiling benzyl benzoate and acenaphthene (F. D. Hartley and F. Lord, of these Laboratories, personal communication). Polymer from *p*-xylylene dichloride ("Wurtz polymer") was not completely soluble, as described above. Both Wurtz and pyrolysis polymer were insoluble in common organic solvents.

*Degradative oxidation of pyrolysis polymer*. Polymer (samples **1**—**3**) freed from substances of low molecular weight by chloroform extraction (Part I) was unchanged by boiling 5N-nitric acid for 24 hr. The polymer (2·25 g.) was heated in boiling glacial acetic acid under a reflux condenser, and *ca.* 0·3-g. portions of chromium(VI) oxide added until spontaneous oxidation ceased. A further portion of oxidant was added, and the mixture boiled for 15 min., but chromate was still present. The mixture was poured into water (250 c.c.) and filtered. The residue was washed free from chromium with water, stirred with excess of dilute aqueous ammonia, and filtered. The residue was unchanged polymer (1·15 g.). The filtrate was acidified, and the precipitate collected (1·1 g.) and converted into methyl ester by methanol–sulphuric acid. The esters were largely dimethyl terephthalate, m. p. and mixed m. p. 140°, which contained 0·1% of dimethyl *iso*phthalate. The latter was estimated by infra-red spectrometry after separation of the terephthalate by *cyclo*hexane.

*Separation of the Polymorphic Forms of the Polymer*

(*a*) A sample of pyrolysis polymer was examined and a single piece of film selected. This was cut in two pieces and one piece reserved as a control (sample **20**). The other piece was dissolved in hot benzyl benzoate, and the solution cooled. A sludge separated and was filtered off, washed with benzene, ethanol, and then dry ether, and dried on the filter to give sample **21**. The *X*-ray photograph of polymer sample **20** showed the usual outer and inner rings of spacing **3·9** and **5·3** Å with a weak middle ring of spacing **4·4** Å. That of sample **21** showed a predominantly strong ring at **4·4** Å with a number of weaker ones. This form, characterised by the strong ring due to a **4·4** Å spacing, is designated β-*lin*-poly-*p*-xylylene.

(*b*) Polymer sample **7** was finely ground in a mortar and put in two test-tubes in an oil-bath at **200°**. After **1** hr. one tube was withdrawn and plunged into an oil-bath at room temperature to give sample **11**. The other tube was annealed by allowing the oil-bath to cool to room temperature during **1** hr., giving sample **12**. The *X*-ray photographs of samples **11** and **12** were identical and resembled that of sample **7**.

(*c*) Polymer sample **7** (**6·6** g.) was ground in a mortar and extracted with chloroform (Soxhlet) for **5½** hr. The extract was yellow. On removal of the chloroform there remained a yellow solid (**0·2** g.; sample **13**), m. p. **184—220°**, melting to a viscous liquid. The polymer remaining after extraction (sample **16**) appeared unchanged and this was confirmed by its *X*-ray diffraction pattern. However, sample **13**, the extract, showed only the outer and the inner diffraction ring, corresponding to spacings of **3·9** and **5·3** Å. This form, characterised by these two rings, is designated α-*lin*-poly-*p*-xylylene. A portion of sample **13** was melted in an air-bath at **240°** and left to cool to give sample **14**. Sample **14** showed a change in internal structure, as in its diffraction pattern the middle ring, corresponding to **4·4** Å, had appeared and was faintly visible. Accordingly, a further portion of sample **13** was melted, held at **300°** for **2** min., and allowed to solidify during **5** min., giving sample **15**. In this case the amount of change was greater, the middle ring on the diffraction pattern having become almost as intense as the other two rings. The diffraction patterns of samples **13**, **14**, and **15** are reproduced in the Plate. A further portion of sample **13** was dissolved in boiling benzyl benzoate and precipitated on cooling. The sludge was filtered off, washed with benzene, ethanol, and ether, and spread on a microscope slide to dry. After **4** weeks at room temperature it was still wet with benzyl benzoate and so it was finally dried at **84°** in an oven (sample **17**). Its diffraction pattern was similar to that of sample **13**. Sample **17**, m. p. **217°**, was melted in a flame and immediately cooled by spraying the tube with ethanol to give sample **18**. The *X*-ray photograph of sample **18** showed that the middle ring had appeared in considerable strength.

(*d*) Wurtz polymer, sample **5** (**10·4** g.), was extracted for **24** hr. with chloroform (Soxhlet). There was obtained a yellow solid extract (**0·07** g.; sample **19**). The *X*-ray photograph of this product resembled that of sample **30** and also bore certain similarities to the powder photograph of **4** : **4′**-dimethyldibenzyl.

(*e*) Pyrolysis polymer was extracted with chloroform as in Part I. The extracted polymer (sample **22**, **4·85** g.) was dissolved in boiling benzyl benzoate (**85** c.c.). A few lumps of swollen gel which were difficult to dissolve were removed with forceps. The solution was left to cool, and then filtered, and the residue washed with cold benzene, ethanol, and ether to yield **4·1** g. of a brown powder (sample **23**). This was extracted with chloroform for several hours (Soxhlet). The extract, sample **24** (**0·1** g.), was a brown solid. Three portions of the extracted matter (sample **26**) were melted in test-tubes with a free flame; one was left to cool in air (sample **27**), one was left to cool wrapped in cotton-wool (sample **28**), and the last quenched by plunging into cold water (sample **29**). *X*-Ray examination of each of these samples showed the following sequence of changes. Sample **22**, the parent sample, showed a preponderance of β-structure, *i.e.*, the middle ring of the diffraction pattern was several times more intense than either of the other two. Sample **23** was almost completely the β-structure, as the rings due to the α-structure had largely disappeared. Sample **24** was completely α-, with a little amorphous matter, but sample **25** was largely β-, with a trace of α-structure. Sample **26** was largely β-, as also were samples **27**, **28**, and **29**, but these three samples had a greater degree of crystallinity than **26**, as shown by an increase in the sharpness of the rings.

(*f*) Wurtz polymer, sample **16**, was placed in a Carius tube which was then flushed three times with nitrogen, evacuated, and sealed. On being heated in an air-bath at **430°** the solid shrank from the walls of the tube and did not melt. The air-bath was removed, and the polymer partially melted with a free flame. The polymer was removed and showed a skin of melted and resolidified polymer (sample **34**), then a circular zone of sintered material (sample **35**), and finally a core of loose powder. Both samples **34** and **35** were swollen by boiling benzyl

benzoate, as was sample **16**. This melting treatment was shown by the diffraction patterns to result in the complete conversion of a mixture of the α- and β-structures into the β-structure.

X-*Ray Experimental Procedure*.—Each sample was photographed in an *X*-ray diffraction camera on a flat film placed at 2·90 cm. from the specimen, which was powdered and pressed by hand into a $\frac{1}{16}$″ hole in a piece of 0·03″ celluloid, and mounted on the end of a 0·05 × 5 cm. lead-glass collimator. Exposure times were generally 2 hr. with a tube current of 20 mA at 50 kv. Although the majority of the photographs were taken for qualitative comparison purposes only (see Table 5), those of samples 17, 27, and 38 were calibrated and measured accurately in order to obtain the unit cell dimensions of polyphenylene and of the α- and the β-form of *lin*-poly-*p*-xylylene.

*Structures of the Polymers*.—In general it is not feasible to determine the crystalline structure of a complex compound from its *X*-ray powder photograph. The problem is especially difficult in the case of polymers on account of the relatively small number of reflexions. In cases where well-oriented specimens are obtainable, *e.g.*, nylon, *X*-ray photographs comparable with those from single crystals can be taken, and the interpretation of these is straightforward (Bunn and Garner, *Proc. Roy. Soc.*, 1947, *A*, **189**, 39). The *lin*-poly-*p*-xylylene polymers, however, are of low molecular weight and show no tendency to form films or fibres; neither have sufficiently large crystals for single-crystal photographs been grown, and so only *X*-ray powder photographs were obtainable. The interpretation of these was simplified by the existence of a series of compounds which are closely related to the polymers and which gave somewhat similar powder photographs; in this way unit cell dimensions for the polymers were found which were related to those of the monomeric compounds. By analogy, structures were then postulated for the polymers.

α-lin-*Poly*-p-*xylylene*. The powder photograph of sample 17 bore certain resemblances to that of 4 : 4′-dimethyldibenzyl; the two strong rings (Photograph *C*, on Plate) were similar, both in position and intensity, to two rings on the powder photograph of 4 : 4′-dimethyldibenzyl. As there was a correspondence of the same kind between the photographs of the β-polymer and diphenyl, it was thought reasonable to investigate the relation between the structures of the α-polymer and 4 : 4′-dimethyldibenzyl. The structure of 4 : 4′-dimethyldibenzyl was not known, and it was necessary to work it out. This was done on the basis of structural similarity between it and the closely related iso-structural series comprising dibenzyl, stilbene, tolane, and *trans*-azobenzene (Robertson, Prasad, and Woodward, *Proc. Roy. Soc.*, 1936, *A*, **154**, 187). The unit-cell dimensions of these compounds, together with those of the α-polymer and 4 : 4′-dimethyldibenzyl, are shown in Table 1.

TABLE 1. *Crystal structures related to* α-lin-*poly*-p-*xylylene*.

| Unit-cell dimensions | *a*, Å | *b*, Å | *c*, Å | *β* |
|---|---|---|---|---|
| α-*lin*-Poly-*p*-xylylene | 11·68 | 6·10 | 9·16 | 102½° |
| 4 : 4′-Dimethyldibenzyl | 2 × 11·68 | 6·10 | 9·16 | 100½ |
| Dibenzyl | 12·77 | 6·12 | 7·70 | 116 |
| Stilbene | 12·35 | 5·70 | 2 × 7·96 | 114 |
| Tolane | 12·75 | 5·73 | 2 × 7·83 | 115 |
| *trans*-Azobenzene | 12·20 | 5·77 | 2 × 7·70 | 114 |

The relationship of the last four compounds with 4 : 4′-dimethyldibenzyl is dealt with fully in the paper describing its structure (Brown, *Acta Cryst.*, 1953, in the press); the comparison between the α-form of the polymer and 4 : 4′-dimethyldibenzyl is made here. The powder photograph was indexed by Ito's method ("*X*-Ray Studies on Polymorphism," Maruzen Co. Ltd., Tokyo, 1950), and the unit cell reduced by Delaunay's method (*Z. Krist.*, 1933, **84**, 132). Before the limit of reduction was reached, it was found that one representation of the lattice corresponded very closely with that of 4 : 4′-dimethyldibenzyl. This is the monoclinic cell shown in Table 1, approximately half the size of the body-centred 4 : 4′-dimethyldibenzyl cell. The indexing of the reflexions of the powder photographs of the two compounds is shown in Table 2.

Allowance being made for the doubling of *a*, and consequently *h*, owing to the body-centring of the dimethyldibenzyl lattice, the strong reflexions on each are seen to correspond. Plane (110) which is strong in the α-polymer is absent from the dimethyldibenzyl because the corresponding plane (210) is a forbidden reflexion owing to body-centring. The two strong planes in the α-polymer (110) and (20$\bar{2}$) give a rough indication of the orientation of the molecular chains, and on this basis an approximate structure can be postulated, as shown in Fig. 1. This is, of course, in no sense an accurate structure determination as would be evident from atomic co-ordinates and lists of structure amplitudes; such would indeed be pressing the

TABLE 2. *Comparison of powder photographs of* 4 : 4′*-dimethyldibenzyl and* α-lin-*poly*-p-*xylylene.*

| 4 : 4′-Dimethyldibenzyl | | | | | | α-*lin*-Poly-*p*-xylylene | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *hkl* | *d* (Å) | *I* | *hkl* | *d* (Å) | *I* | *hkl* | *d* (Å) | *I* | *hkl* | *d* (Å) | *I* |
| (200) | 11·50 | m | (31$\bar{2}$) | 3·48 | m | (110) | 5·38 | s | (11$\bar{2}$) | 3·64 | m |
| (400) | 5·75 | m | (312) | 3·10 | | (011) | 5·06 | m | (020) | 3·06 | w |
| (011) | 5·05 | v.s. | (51$\bar{2}$) | 3·07 | m.s. | (111) | 4·42 | w | (12$\bar{1}$) | 2·84 | m |
| (002) | 4·51 | m | (020) | 3·05 | | (21$\bar{1}$) | 3·98 | s | (22$\bar{1}$) | 2·64 | v.w. |
| (20$\bar{2}$) | 4·49 | | (710) | 2·89 | m | (20$\bar{2}$) | 3·95 | | (21$\bar{2}$) | 2·41 | v.w. |
| (41$\bar{1}$) | 4·00 | s | (41$\bar{3}$) | 2·61 | m | | | | | | |
| (40$\bar{2}$) | 3·91 | s | (613) | 2·05 | w | | | | | | |
| (11$\bar{2}$) | 3·66 | m | | | | | | | | | |

analogy further than the *X*-ray diffraction photographs from this class of substance justify, but it is a reasonable interpretation of the data available, and one which appears to fit all the facts at present known. There is no evidence of monoclinic symmetry; the simplest unit cell is triclinic, but the monoclinic representation is retained in order to show the relation to 4 : 4′-dimethyldibenzyl. It is concluded that the α-form of the polymer crystallises in a very similar manner to 4 : 4′-dimethyldibenzyl and has the same characteristic " stepped " structure.

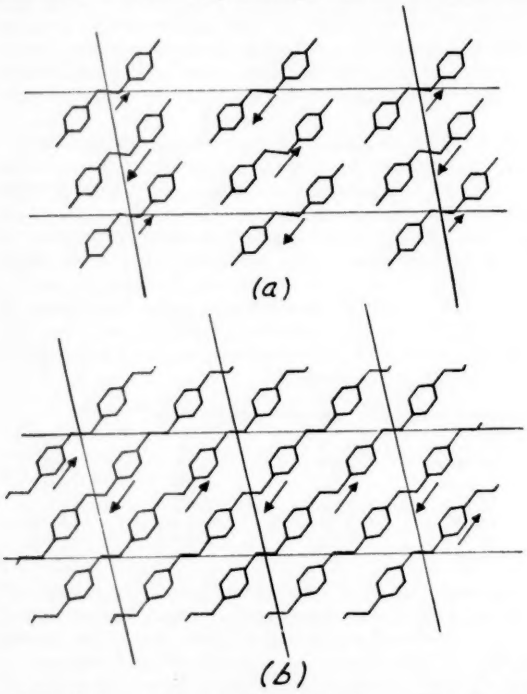



FIG. 1. *Diagrammatic projection of crystal structures of* (*a*) 4 : 4′*-dimethyldibenzyl and* (*b*) α-lin-*poly*-p-*xylylene.*

*The arrows indicate the direction of inclination with respect to the plane of the paper.*

β lin-*Poly*-p-*xylylene and polyphenylene.* The *X*-ray powder photograph of the β-form of the polymer (sample No. 27) showed, as its outstanding characteristic feature, one strong ring at a spacing of 4·4 Å, together with a number of less intense ones. A powder photograph of diphenyl taken under similar conditions also exhibited a very strong ring at a similar, although not identical, spacing, and it was suggested that the similarity of the two diffraction patterns might be due to a resemblance of molecular packing in the two substances. If this were so, the β-form of the polymer would fall into a crystallographic series of a number of hydrocarbons whose structures are well known (Table 3).

The molecular packing of the first three members of this series is identical with respect to the *a* and *b* axes, *c* being sufficient to accommodate the length of the molecule. The hypothesis for the polymers is that the cross-sectional packing shall again be the same, but that [*c*] should be the length of one repeat unit in the molecular chain. With unit cells derived in this way, the indexing of the photographs is as shown in Table 4.

TABLE 3. *Crystal structures related to* β-lin-*poly*-p-*xylylene*.

| Unit-cell dimensions | *a*, Å | *b*, Å | *c*, Å | β |
|---|---|---|---|---|
| Diphenyl | 8·11 | 5·67 | 9·57 | 94½° |
| Terphenyl | 8·08 | 5·60 | 13·59 | 92 |
| Quaterphenyl | 8·14 | 5·64 | 18·4 | 97 |
| *β-lin*-Poly-*p*-xylylene | 8·10 | 5·25 | 6·53 | 95 |
| Polyphenylene | 8·10 | 5·35 | 4·22 | 95 |

TABLE 4. *Comparison of powder photographs of diphenyl, polyphenylene, and* β-lin-*poly*-p-*xylylene*.

| Diphenyl | | | Polyphenylene | | | *β-lin*-Poly-*p*-xylylene | | |
|---|---|---|---|---|---|---|---|---|
| *hkl* | *d*, Å | *I* | *hkl* | *d*, Å | *I* | *hkl* | *d*, Å | *I* |
| (001) | 9·53 | w | (110) | 4·47 | s | (001) | 6·53 | w |
| (110) | 4·64 | s | (201) | 4·22 | w | (10$\bar{1}$) | 5·32 | w |
| (11$\bar{1}$) | 4·25 | m | (10$\bar{1}$) | 3·84 | w | (101) | 4·88 | w |
| (111) | 4·10 | w | (11$\bar{1}$) | 3·12 | w | (110) | 4·40 | s |
| (20$\bar{1}$) | 3·83 | m | (020) | 2·68 | w | (200) | 4·05 | w |
| (201) | 3·62 | w | | | | (111) | 3·58 | w |
| (20$\bar{2}$) | 3·15 | m | | | | (201) | 3·32 | m |
| | | | | | | (102) | 2·95 | m |
| | | | | | | (120) | 2·51 | w |
| | | | | | | (121) | 2·32 | w |
| | | | | | | (22$\bar{1}$) | 2·12 | w |
| | | | | | | (400) | 2·02 | w |
| | | | | | | (22$\bar{3}$) | 1·87 | w |

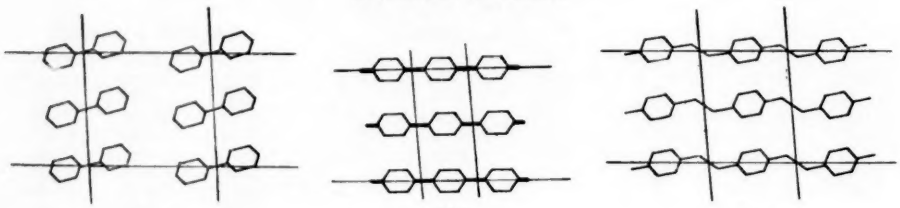
TABLE 5. *Summary of samples and X-ray photographs.*

| Sample No. | Description | Intensity of rings: inner, 5·3 Å | middle, 4·4 Å | outer, 3·9 Å |
|---|---|---|---|---|
| 1 | Pyrolysis | m | m | m |
| 2 | Pyrolysis | s | w | s |
| 3 | Pyrolysis | m | s | m |
| 4 | Wurtz reaction in toluene | | * | |
| 5 | Wurtz reaction in *p*-xylene | s | w | s |
| 6 | Wurtz reaction in *p*-xylene | m | m | m |
| 7 | Wurtz reaction in *p*-xylene | m | m | m |
| 8 | Wurtz reaction in dioxan | w | s | w |
| 9 | Wurtz reaction in dioxan | s | m | s |
| 10 | Wurtz reaction in ditolylmethane | | * | |
| 11 | Sample 7 heated to 200°, quenched | m | m | m |
| 12 | Sample 7 heated to 200°, annealed | m | m | m |
| 13 | Chloroform extract of Sample 7 | s | — | s |
| 14 | Sample 13 melted at 240° | s | w | s |
| 15 | Sample 13 heated to 300° for 2 min. | s | m | s |
| 16 | Sample 7 after extraction by chloroform | m | m | m |
| 17 | Sample 13 recryst. from benzyl benzoate | s | — | s |
| 18 | Sample 17 melted | m | s | m |
| 19 | Chloroform extract of Sample 5 | s | w | s |
| 20 | Pyrolysis | s | w | s |
| 21 | Sample 20 recryst. from benzyl benzoate | — | s | — |
| 22 | Pyrolysis | m | s | m |
| 23 | Sample 22 recryst. from benzyl benzoate | w | s | w |
| 24 | Chloroform extract of Sample 23 | s | — | s |
| 25 | Sample 24 melted | w | s | w |
| 26 | Sample 23 after extraction by chloroform | w | s | w |
| 27 | Sample 26 melted | w | s | w |
| 28 | Sample 26 melted | w | s | w |
| 29 | Sample 26 melted | w | s | w |
| 30 | Wurtz in *p*-xylene at low concentration | s | w | s |
| 31 | As Sample 30, but higher mol. wt. | s | w | s |
| 32 | Phenethylchloride: Friedel–Crafts | | * | |
| 33 | Polyphenylene butylene | | * | |
| 34 | Sample 16 heat-treated | — | s | — |
| 35 | Sample 16 sintered | — | s | — |
| 36 | Polyphenylene | | * | |
| 37 | Sample 36 melted | | * | |
| 38 | Polyphenylene | — | s | — |

* Amorphous.

On the basis of this indexing, the (110) plane gives the outstandingly strong reflexion in all three cases. This plane depends on the lengths of (*a*) and (*b*), and since these are very similar in all these compounds (Table 3), it would seem that they are determined by the dimensions of the benzene rings and how closely they can pack together. The molecules of diphenyl are known to be planar, and as the lateral dimensions are so similar it is most likely that the molecular chains of the polymers polyphenylene and β-*lin*-poly-*p*-xylylene will be planar also. The molecular arrangements of these three related substances are shown in Fig. 2.

FIG. 2. *Digrammatic projection of crystal structures of* (*a*) *diphenyl,* (*b*) *polyphenylene, and* (*c*) β-lin-*poly*-p-*xylylene.*




The configuration around the aliphatic carbon atoms in the β-form of the polymer is uncertain. The whole molecular chain is, in all probability, planar, but if the central C–C bond is single, the usual tetrahedral angle may be expected. If there is a loss of hydrogen, as Goldfinger suggests, the angle will be greater than this. Such small differences can scarcely be detected on the basis of unit-cell measurements. It is, however, plain that this type of molecular packing must be correct as it is the only one which accounts for the diffraction pattern.

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## 650. *The Crystal Structure of Di-*m*-xylylene.*

By C. J. BROWN.

The atomic arrangement in crystals of di-*m*-xylylene has been worked out completely, using *X*-ray diffraction data and three-dimensional Fourier syntheses. The molecules are centrosymmetric and the two halves form a stepped system. The benzene rings are boat-shaped to achieve adequate separation between the central carbon atoms which are 2·69 Å apart. The mean aromatic carbon to carbon bond-length is 1·386 Å, and the aliphatic 1·543 Å.

DURING the determination of the structure of di-*p*-xylylene (Brown, *J.*, 1953, 3265, 3270) attention was directed to the isomeric compounds di-*o*-xylylene and di-*m*-xylylene. Di-*o*-xylylene had been prepared by Baker, Banks, Lyon, and Mann (*J.*, 1945, 27), but the *X*-ray work by Davidson and Perutz proceeded no further than the determination of the unit-cell dimensions and space-group. Di-*m*-xylylene had been prepared originally by Pellegrin (*Rec. Trav. chim.*, 1899, **18**, 458), and this work has been confirmed more recently by Baker, McOmie, and Norman (*Chem. and Ind.*, 1950, 77; *J.*, 1951, 1114). It was suggested, in discussion with Professor Baker, that an *X*-ray investigation of the structure of di-*m*-xylylene would throw light on the stereochemistry of the molecule, and this work has been carried out on samples of his preparations.

The benzene ring has long been regarded as a regular, plane hexagon of carbon atoms. There is evidence that in a number of fused benzene rings, the regularity is destroyed, *e.g.*, in coronene (Robertson and White, *J.*, 1945, 607), but in all simple aromatic compounds no great divergence from regularity is expected. It was pointed out, however, by Cook (*Ann. Reports*, 1942, **39**, 173) that this would lead to abnormally close approaches between atoms in certain cases, particularly 3 : 4-5 : 6-dibenzophenanthrene, and the crystal-structure determination of one form of this compound (McIntosh, Robertson, and Vand,

*Nature*, 1952, **169**, 322) confirms that there is considerable distortion in the molecule to avoid clashing between neighbouring non-bonded carbon atoms. A similar phenomenon would be expected in the case of di-*m*-xylylene where, if all the bond lengths and inter-bond angles possessed standard values, the central non-bonded carbon atoms would be approximately 1·54 Å apart. In order to find out the true distance between these atoms, and how the remainder of the molecule would be distorted, the crystal-structure determination was commenced.

The unit-cell dimensions are $a = 12{\cdot}22$, $b = 8{\cdot}28$, and $c = 5{\cdot}82$ Å, and the angle $\beta = 93° 18'$. On the assumptions of two molecules per unit cell and a molecular weight (for $C_{16}H_{16}$) of 208·1, the calculated specific gravity should be 1·176; that observed was 1·178. Absent reflexions were $\{0k0\}$ for $k$ odd, and $\{h0l\}$ for $h$ odd, so the space-group was fixed unambiguously as $P2_1/a$ ($C_{2h}^5$). As this space-group has a four-fold general position, it

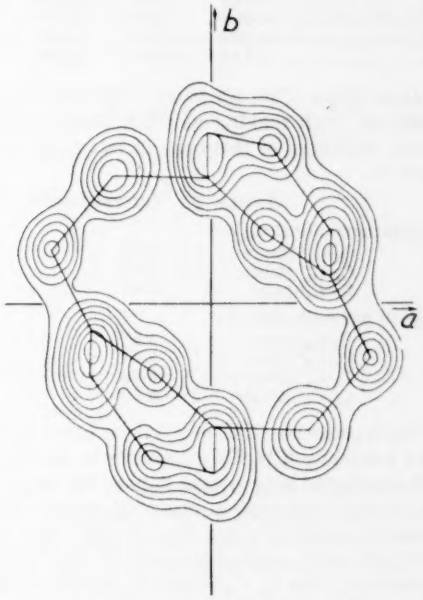



FIG. 1. *Electron-density map of di-*m*-xylylene obtained by projection along* c *axis.*

followed that the molecules of di-*m*-xylylene possessed centres of symmetry and that the centres of molecules would coincide with centres of symmetry in the unit cell.

Despite the close similarity between the cell dimensions of di-*m*-xylylene and of dibenzyl (Jeffrey, *Proc. Roy. Soc.*, 1947, *A*, **188**, 222) as well as a resemblance between the general shapes of the molecules, there is no correspondence between their arrangement in the unit cell, and attempts to solve the structure by analogy were unsuccessful. Indeed, all the usual methods of finding a suitable trial structure, such as Patterson syntheses, molecular structure factors, and inequalities were unsuccessful. The approach which eventually led to a solution was a graphical method in which the planes giving strongest reflexions were represented by lines in a scale diagram and various orientations of a molecular model were tried in order to place individual atoms in phase with respect to these strong planes. Taken in conjunction with the fact that a group of strong planes lying almost parallel to each other, *i.e.*, $(43\bar{1})$, $(43\bar{2})$, $(42\bar{1})$, $(32\bar{1})$, $(22\bar{1})$, and $(44\bar{1})$, appeared to coincide roughly with a prominent plane in the molecule, this method gave a molecular arrangement where a moderate number of calculated structure amplitudes agreed with the experimental values.

From this point, refinement of the atomic co-ordinates proceeded in the usual way. Two-dimensional Fourier syntheses were used for the $b$ and $c$ axis projections, neither of which was entirely free from overlapping atoms. The electron-density map obtained by

plotting the best *c* projection is shown in Fig. 1. Following these, three-dimensional Fourier syntheses were used, first with a limited number of terms, and then more being gradually introduced as their phases were determined until all the 1200 were included. The progress of the refinement was followed by calculating the residual $R = \frac{\Sigma|F(exp.)| - |F(calc.)|}{\Sigma F(exp.)}$ which, for the last three sets of structure amplitudes had values of 0·26, 0·208, and 0·163. The last synthesis resulted in no changes of phase of the calculated structure amplitudes, and the refinement was then considered to be complete. The resulting atomic co-ordinates are listed in Table 1.

TABLE 1. *Atomic co-ordinates.*

| | *x* | *y* | *z* | | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|
| $C_1$ ..... | 0·882 | 0·231 | 0·817 | $C_5$ ..... | 0·198 | 0·904 | 0·111 |
| $C_2$ ..... | 0·988 | 0·232 | 0·978 | $C_6$ ..... | 0·999 | 0·319 | 0·179 |
| $C_3$ ..... | 0·068 | 0·119 | 0·942 | $C_7$ ..... | 0·081 | 0·285 | 0·351 |
| $C_4$ ..... | 0·142 | 0·067 | 0·119 | $C_8$ ..... | 0·149 | 0·156 | 0·322 |

*Description of the Structure.*—The crystal structure of di-*m*-xylylene comprises discrete molecules, each making van der Waals contacts with eight others. There are 40 interatomic distances of this type of less than 4 Å between molecules, and these are shown in Table 2.

TABLE 2. *Intermolecular ("van der Waals") distances* (Å).

| | | | |
|---|---|---|---|
| With molecule along *a* : | | With molecule along *c* : | |
| $C_3$–$C_5'$ (four) | 3·74 | $C_7$–$C_1$ (four) | 3·77 |
| $C_4$–$C_5'$ (four) | 3·71 | $C_7$–$C_2$ (four) | 3·96 |
| $C_4$–$C_1$ (four) | 3·88 | $C_7$–$C_3$ (four) | 3·72 |
| With molecule along *b* : | | $C_8$–$C_3$ (four) | 3·81 |
| $C_2$–$C_2'$ (two) | 3·64 | | |
| $C_6$–$C_6'$ (two) | 3·65 | | |
| $C_2$–$C_6'$ (four) | 3·70 | | |
| $C_1$–$C_6'$ (four) | 4·00 | | |

Each molecule of di-*m*-xylylene has a centre of symmetry, and consists of two benzene rings joined by $\cdot CH_2 \cdot CH_2 \cdot$ linkages in the *meta*-positions. This has the effect of producing a 10-membered ring system flanked by two 6-membered benzene rings. The benzene rings are located step-wise in order to permit adequate clearance between the central carbon atoms ($C_3$ and $C_3'$; see Fig. 2) and their attached hydrogen atoms. Even then, were strict planarity and regularity of the hexagonal ring systems and substituents to be maintained, the $C_3$–$C_3'$ distance would be almost the same as $C_1$–$C_5' = 1{\cdot}56$ Å. This is impossibly close for non-bonded carbon atoms; and the situation is relieved by a distortion of the rings. Carbon atom 3 is displaced out of the mean plane of $C_2C_4C_6C_8$ by 0·143 Å, and the substituent methylene carbon atoms 1 and 5 by approximately 0·4 Å, so that the substituting bonds make angles of approx. 15° with the mean plane of the ring (Fig. 3). A secondary effect is that the carbon atom 7 at the far end of the benzene ring is also displaced out of the plane by 0·042 Å. The result of this distortion is to increase the distance between $C_3$ and $C_3'$ to 2·689 Å. The bond lengths and inter-bond angles are listed in Table 3, and are shown diagrammatically in Fig. 2.

TABLE 3. *Bond lengths* (Å) *and inter-bond angles.*

| | |
|---|---|
| $C_1$–$C_3' = 1{\cdot}559$ | $C_4$–$C_5 = 1{\cdot}515$ |
| $C_1$–$C_2 = 1{\cdot}554$ | |
| Mean aliphatic C–C = 1·543 ± 0·013 Å | |
| $C_2$–$C_3 = 1{\cdot}378$ | $C_6$–$C_7 = 1{\cdot}404$ |
| $C_3$–$C_4 = 1{\cdot}399$ | $C_7$–$C_8 = 1{\cdot}369$ |
| $C_2$–$C_6 = 1{\cdot}374$ | $C_8$–$C_4 = 1{\cdot}391$ |
| Mean aromatic C–C = 1·386 ± 0·008 Å | |

| | |
|---|---|
| $C_2\widehat{C_1}C_5' = 110° 48'$ | $C_4\widehat{C_5}C_1' = 109° 39'$ |
| Mean tetrahedral angle = 110° 18′ | |
| $C_2\widehat{C_2}C_6 = 116° 42'$ | $C_3\widehat{C_4}C_5 = 121° 45'$ |
| $C_1\widehat{C_2}C_6 = 123° 36'$ | $C_8\widehat{C_4}C_5 = 119° 32'$ |
| $C_1\widehat{C_2}C_3 = 118° 38'$ | $C_5\widehat{C_6}C_7 = 122° 14'$ |
| $C_2\widehat{C_3}C_4 = 122° 16'$ | $C_6\widehat{C_7}C_8 = 118° 48'$ |
| $C_3\widehat{C_4}C_8 = 117° 55'$ | $C_7\widehat{C_8}C_4 = 120° 40'$ |
| Mean hexagonal angle = 120° 13′ ± 1° 16′ | |

The equation of the mean plane through $C_2C_4C_6C_8$ was calculated, by the method of least squares, to be $x + 0{\cdot}952y - 0{\cdot}624z = 1{\cdot}782$. The distances (in Å) of the various carbon atoms from this plane are:

| | | | |
|---|---|---|---|
| $C_1$, −0·448 | $C_3$, +0·143 | $C_5$, −0·368 | $C_7$, +0·042 |
| $C_2$, −0·009 | $C_4$, +0·006 | $C_6$, +0·007 | $C_8$, −0·005 |

The angle which the $C_1$–$C_2$ bond makes with this mean plane is 16° 45′, and that made by the $C_4$–$C_5$ bond is 14° 4′.

No account has been taken of the hydrogen atoms at any stage of this work, nor have any atomic co-ordinates been calculated for them.

Although hydrocarbons are possibly one of the least interesting and least reactive classes of organic compounds, more attention appears to have been paid to them by *X*-ray analysts than to any other. Many of them have been investigated to a preliminary stage by *X*-ray

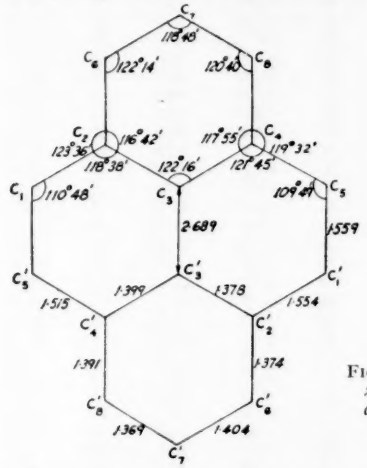
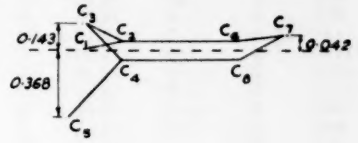



FIG. 2. *Diagram of molecule of di-m-xylylene showing bond lengths (in Å) and inter-bond angles.*

FIG. 3. *Showing the distortion of the benzene ring in di-m-xylylene from planarity.*




diffraction, and the crystal structures of about 20 of them have been determined. Of these, at least 7 have been refined by three-dimensional Fourier methods, and it can be expected that the resulting bond lengths are fairly accurate. Table 4 lists the C–C bond lengths obtained in these analyses. It shows that the values obtained for these bond

TABLE 4. *Mean carbon-to-carbon bond lengths* (Å) *in aromatic hydrocarbons.*

| | Aliphatic | Aromatic |
|---|---|---|
| Naphthalene [1] | — | 1·391 ± 0·015 |
| Anthracene [2] | — | 1·397 ± 0·016 |
| Dibenzyl [3] | 1·49 | 1·373 ± 0·008 |
| 1 : 2 : 3 : 4-Tetraphenyl*cyclo*butane [4] | 1·537 | 1·388 ± 0·009 |
| Bisdiphenylene-ethylene [5] | 1·48 | 1·40 |
| Di-*p*-xylylene [6] | 1·544 | 1·395 |
| Di-*m*-xylylene | 1·543 ± 0·013 | 1·386 ± 0·008 |

(The C–C value in diamond is 1·5445 Å.)

[1] Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 238. [2] Sinclair, Robertson, and Mathieson, *ibid.*, 1950, **3**, 251. [3] Jeffrey, *loc. cit.* [4] Dunitz, *Acta Cryst.*, 1949, **2**, 1. [5] Fenimore, *ibid.*, 1948, **1**, 295. [6] Brown, *J.*, 1953, 3265.

lengths in di-*m*-xylylene agree well with those found in other accurate analyses. It is interesting that the benzene ring, normally hexagonal, can be distorted to such an extent without interfering appreciably with the interatomic distances.

## EXPERIMENTAL

The sample of di-*m*-xylylene was prepared by Professor W. Baker and Miss J. M. Norman by the action of sodium on *m*-xylylene dibromide. Good crystals were readily obtained by evaporation of an alcoholic solution; they were prismatic and roughly equidimensional in shape.

TABLE 5. *Experimental and calculated structure amplitudes.*

| *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 000 | — | +224 | 006 | 4 | + 4 | 712 | 6 | − 4 | 016 | 3 | + 2 |
| 200 | 40 | + 40 | 206 | 4 | + 5 | 10,12 | 2 | + 1 | 116 | 2 | + 2 |
| 400 | 17 | − 16 | 406 | 2 | − 2 | 11,12 | 2 | − 1 | 516 | 1 | − 1 |
| 600 | 13 | + 13 | 606 | 2 | + 2 | 13,12 | 2 | + 1 | 616 | 1 | + 1 |
| 800 | 4 | + 7 | 806 | 3 | + 4 | 14,12 | 1 | + 2 | 716 | 2 | + 2 |
| 10,00 | 2 | + 4 | $60\bar{7}$ | 1 | + 1 | 13,$1\bar{3}$ | 1 | + 1 | $61\bar{7}$ | 1 | + 2 |
| 12,00 | 2 | + 3 | $20\bar{7}$ | 1 | − 1 | 11,$1\bar{3}$ | 3 | + 3 | $31\bar{7}$ | 2 | − 1 |
| 14,00 | 5 | + 6 | 007 | 1 | − 1 | 10,$1\bar{3}$ | 2 | + 1 | $21\bar{7}$ | 1 | 0 |
| 14,0$\bar{1}$ | 2 | + 2 | 207 | 1 | − 1 | 91$\bar{3}$ | 2 | + 1 | 017 | 1 | 0 |
| 10,0$\bar{1}$ | 5 | + 6 | 110 | 26 | +29 | 81$\bar{3}$ | 6 | + 6 | 117 | 1 | + 1 |
| 80$\bar{1}$ | 5 | + 5 | 210 | 18 | −19 | 71$\bar{3}$ | 3 | + 4 | 217 | 1 | + 2 |
| 60$\bar{1}$ | 3 | − 1 | 310 | 37 | −37 | 61$\bar{3}$ | 2 | + 2 | 417 | 1 | + 1 |
| 40$\bar{1}$ | 2 | + 2 | 410 | 14 | −14 | 51$\bar{3}$ | 6 | − 5 | 020 | 48 | −48 |
| 20$\bar{1}$ | 76 | + 76 | 510 | 2 | − 1 | 41$\bar{3}$ | 9 | −10 | 120 | 7 | − 8 |
| 001 | 64 | + 64 | 610 | 3 | + 3 | 31$\bar{3}$ | 1 | + 1 | 220 | 42 | −38 |
| 201 | 37 | − 37 | 810 | 1 | − 1 | 21$\bar{3}$ | 20 | −22 | 320 | 27 | −21 |
| 401 | 29 | + 23 | 910 | 5 | − 4 | 11$\bar{3}$ | 9 | + 9 | 420 | 3 | − 5 |
| 601 | 23 | + 24 | 10,10 | 10 | +12 | 013 | 8 | + 8 | 520 | 11 | + 9 |
| 801 | 1 | + 3 | 11,10 | 3 | − 3 | 113 | 1 | − 3 | 620 | 2 | − 2 |
| 14,01 | 3 | + 3 | 12,10 | 10 | + 8 | 213 | 11 | −14 | 720 | 2 | − 1 |
| 14,0$\bar{2}$ | 1 | − 3 | 13,10 | 1 | 0 | 313 | 11 | +12 | 820 | 12 | − 9 |
| 12,0$\bar{2}$ | 3 | + 4 | 14,10 | 1 | − 2 | 413 | 3 | + 4 | 920 | 10 | − 8 |
| 10,0$\bar{2}$ | 8 | + 8 | 15,10 | 3 | + 2 | 513 | 7 | + 7 | 10,20 | 6 | − 6 |
| 80$\bar{2}$ | 2 | − 4 | 15,1$\bar{1}$ | 4 | + 3 | 615 | 7 | + 7 | 11,20 | 9 | + 7 |
| 60$\bar{2}$ | 7 | − 6 | 14,1$\bar{1}$ | 3 | + 4 | 813 | 1 | + 1 | 12,20 | 2 | − 3 |
| 40$\bar{2}$ | 9 | − 8 | 12,1$\bar{1}$ | 9 | + 8 | 913 | 2 | − 1 | 13,20 | 2 | + 2 |
| 20$\bar{2}$ | 5 | + 11 | 10,1$\bar{1}$ | 1 | + 1 | 10,13 | 3 | + 3 | 15,20 | 2 | − 2 |
| 002 | 6 | − 4 | 91$\bar{1}$ | 1 | + 2 | 11,13 | 2 | − 2 | 15,2$\bar{1}$ | 2 | − 2 |
| 202 | 6 | + 4 | 81$\bar{1}$ | 3 | + 2 | 12,13 | 2 | + 2 | 14,2$\bar{1}$ | 1 | 0 |
| 402 | 34 | + 34 | 71$\bar{1}$ | 3 | − 3 | 13,13 | 2 | + 2 | 13,2$\bar{1}$ | 4 | + 2 |
| 602 | 5 | + 1 | 61$\bar{1}$ | 13 | +10 | 12,1$\bar{4}$ | 2 | − 2 | 12,2$\bar{1}$ | 2 | − 1 |
| 802 | 7 | − 6 | 51$\bar{1}$ | 16 | −16 | 11,1$\bar{4}$ | 3 | + 2 | 11,2$\bar{1}$ | 1 | − 1 |
| 10,02 | 4 | − 6 | 31$\bar{1}$ | 15 | −15 | 10,1$\bar{4}$ | 2 | − 2 | 10,2$\bar{1}$ | 6 | − 4 |
| 12,02 | 2 | − 2 | 21$\bar{1}$ | 27 | +29 | 91$\bar{4}$ | 2 | + 2 | 92$\bar{1}$ | 5 | − 4 |
| 14,02 | 3 | + 3 | 11$\bar{1}$ | 44 | +44 | 81$\bar{4}$ | 3 | + 2 | 82$\bar{1}$ | 5 | − 5 |
| 14,0$\bar{3}$ | 1 | + 1 | 011 | 15 | −19 | 71$\bar{4}$ | 1 | − 1 | 72$\bar{1}$ | 17 | +13 |
| 12,0$\bar{3}$ | 4 | + 5 | 111 | 2 | − 2 | 61$\bar{4}$ | 4 | − 4 | 62$\bar{1}$ | 3 | − 3 |
| 80$\bar{3}$ | 3 | − 4 | 211 | 4 | + 1 | 51$\bar{4}$ | 6 | − 7 | 52$\bar{1}$ | 12 | −14 |
| 60$\bar{3}$ | 4 | − 3 | 311 | 6 | − 9 | 41$\bar{4}$ | 9 | − 8 | 42$\bar{1}$ | 29 | −28 |
| 40$\bar{3}$ | 8 | − 10 | 411 | 11 | − 6 | 31$\bar{4}$ | 4 | + 4 | 32$\bar{1}$ | 39 | −38 |
| 20$\bar{3}$ | 10 | + 10 | 511 | 15 | +14 | 21$\bar{4}$ | 4 | − 3 | 22$\bar{1}$ | 34 | −36 |
| 003 | 1 | + 2 | 611 | 6 | − 6 | 11$\bar{4}$ | 1 | − 1 | 12$\bar{1}$ | 13 | −11 |
| 203 | 2 | + 3 | 711 | 9 | − 8 | 114 | 3 | − 3 | 021 | 3 | − 2 |
| 403 | 10 | + 9 | 811 | 1 | − 1 | 214 | 8 | +11 | 121 | 21 | +16 |
| 603 | 4 | − 6 | 911 | 7 | − 5 | 314 | 9 | + 9 | 221 | 5 | − 1 |
| 803 | 4 | − 5 | 10,11 | 6 | + 4 | 414 | 14 | +16 | 321 | 4 | − 1 |
| 10,03 | 3 | − 4 | 11,11 | 2 | − 1 | 514 | 3 | + 2 | 421 | 5 | − 5 |
| 12,03 | 2 | + 2 | 12,11 | 1 | − 1 | 714 | 3 | − 2 | 521 | 3 | 0 |
| 12,0$\bar{4}$ | 2 | + 1 | 13,11 | 2 | + 2 | 10,14 | 2 | + 2 | 621 | 14 | −13 |
| 10,0$\bar{4}$ | 2 | + 1 | 14,11 | 2 | − 2 | 12,1$\bar{5}$ | 2 | − 3 | 721 | 7 | − 6 |
| 80$\bar{4}$ | 4 | + 5 | 15,11 | 2 | + 1 | 11,1$\bar{5}$ | 2 | + 2 | 821 | 13 | −11 |
| 40$\bar{4}$ | 4 | + 2 | 15,1$\bar{2}$ | 2 | + 2 | 10,1$\bar{5}$ | 2 | + 2 | 921 | 2 | + 4 |
| 20$\bar{4}$ | 7 | + 7 | 14,1$\bar{2}$ | 2 | + 2 | 81$\bar{5}$ | 3 | + 2 | 10,21 | 4 | − 4 |
| 004 | 8 | − 11 | 12,1$\bar{2}$ | 2 | + 1 | 71$\bar{5}$ | 2 | − 2 | 11,21 | 11 | + 9 |
| 204 | 3 | + 5 | 11,1$\bar{2}$ | 4 | + 4 | 61$\bar{5}$ | 3 | − 3 | 14,21 | 1 | + 1 |
| 404 | 12 | + 12 | 91$\bar{2}$ | 1 | − 1 | 31$\bar{5}$ | 1 | + 2 | 15,21 | 1 | + 1 |
| 804 | 2 | − 1 | 81$\bar{2}$ | 11 | +10 | 21$\bar{5}$ | 1 | − 1 | 15,2$\bar{2}$ | 1 | − 1 |
| 12,0$\bar{5}$ | 4 | + 4 | 71$\bar{2}$ | 3 | − 3 | 11$\bar{5}$ | 6 | − 7 | 13,2$\bar{3}$ | 2 | + 1 |
| 10,0$\bar{5}$ | 5 | + 5 | 61$\bar{2}$ | 13 | +13 | 015 | 9 | + 8 | 12,2$\bar{2}$ | 3 | − 3 |
| 80$\bar{5}$ | 4 | + 5 | 51$\bar{2}$ | 4 | − 4 | 215 | 9 | + 9 | 11,2$\bar{3}$ | 1 | − 1 |
| 60$\bar{5}$ | 1 | + 1 | 41$\bar{2}$ | 9 | +11 | 315 | 6 | + 5 | 10,2$\bar{2}$ | 3 | − 3 |
| 40$\bar{5}$ | 3 | + 3 | 31$\bar{2}$ | 2 | + 4 | 415 | 2 | + 2 | 92$\bar{2}$ | 3 | + 3 |
| 20$\bar{5}$ | 3 | − 2 | 21$\bar{3}$ | 2 | 0 | 515 | 2 | − 2 | 82$\bar{2}$ | 1 | + 1 |
| 005 | 1 | − 1 | 11$\bar{2}$ | 19 | +23 | 615 | 2 | − 2 | 72$\bar{2}$ | 7 | + 4 |
| 205 | 13 | + 15 | 012 | 30 | +32 | 815 | 2 | + 2 | 62$\bar{2}$ | 4 | − 3 |
| 405 | 6 | + 6 | 112 | 1 | − 4 | 915 | 2 | + 1 | 52$\bar{2}$ | 19 | −18 |
| 605 | 2 | − 2 | 212 | 5 | − 3 | 10,1$\bar{6}$ | 2 | + 3 | 42$\bar{2}$ | 16 | −15 |
| 805 | 2 | + 2 | 312 | 11 | +11 | 41$\bar{6}$ | 2 | + 2 | 32$\bar{2}$ | 9 | − 8 |
| 10,0$\bar{6}$ | 1 | + 2 | 412 | 17 | −18 | 31$\bar{6}$ | 3 | − 2 | 22$\bar{2}$ | 5 | + 7 |
| 80$\bar{6}$ | 2 | + 2 | 512 | 10 | + 8 | 21$\bar{6}$ | 2 | − 2 | 12$\bar{2}$ | 11 | −13 |
| 60$\bar{6}$ | 2 | + 2 | 612 | 3 | − 5 | 11$\bar{6}$ | 4 | − 4 | 022 | 8 | + 9 |

TABLE 5. (*Continued.*)

| *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 122 | 15 | +15 | 127 | 1 | + 2 | 12,3$\bar{3}$ | 1 | − 1 | 740 | 4 | + 4 |
| 222 | 14 | −14 | 227 | 1 | + 2 | 11,3$\bar{3}$ | 2 | − 2 | 840 | 12 | + 8 |
| 322 | 4 | − 8 | 327 | 2 | + 2 | 83$\bar{3}$ | 5 | + 5 | 940 | 2 | − 1 |
| 422 | 10 | −10 | 427 | 1 | − 2 | 73$\bar{3}$ | 8 | − 8 | 10,40 | 4 | + 4 |
| 522 | 3 | + 3 | 130 | 2 | − 2 | 63$\bar{3}$ | 2 | − 3 | 11,40 | 2 | + 1 |
| 622 | 5 | − 5 | 230 | 22 | −18 | 53$\bar{3}$ | 6 | − 6 | 14,40 | 1 | − 2 |
| 822 | 1 | 0 | 330 | 17 | +17 | 43$\bar{3}$ | 1 | + 3 | 14,4$\bar{1}$ | 1 | − 1 |
| 922 | 2 | + 3 | 430 | 12 | − 9 | 33$\bar{3}$ | 3 | + 3 | 13,4$\bar{1}$ | 2 | + 2 |
| 10,22 | 2 | + 2 | 530 | 2 | + 4 | 23$\bar{3}$ | 6 | + 9 | 12,4$\bar{1}$ | 1 | + 1 |
| 11,22 | 4 | + 3 | 630 | 12 | +12 | 13$\bar{3}$ | 6 | − 5 | 11,4$\bar{1}$ | 3 | + 2 |
| 12,22 | 1 | + 1 | 830 | 8 | − 8 | 033 | 2 | + 5 | 10,4$\bar{1}$ | 3 | + 1 |
| 14,2$\bar{3}$ | 3 | − 3 | 930 | 2 | + 4 | 133 | 11 | −11 | 94$\bar{1}$ | 3 | − 2 |
| 13,2$\bar{3}$ | 1 | + 1 | 10,30 | 4 | − 5 | 233 | 5 | + 5 | 84$\bar{1}$ | 6 | + 5 |
| 12,2$\bar{3}$ | 3 | − 3 | 11,30 | 2 | + 3 | 333 | 5 | − 8 | 74$\bar{1}$ | 6 | + 4 |
| 11,2$\bar{3}$ | 1 | − 1 | 12,30 | 3 | + 2 | 533 | 4 | − 6 | 64$\bar{1}$ | 7 | + 6 |
| 10,2$\bar{3}$ | 3 | + 3 | 13,30 | 1 | + 1 | 633 | 8 | −11 | 54$\bar{1}$ | 4 | + 4 |
| 92$\bar{3}$ | 4 | + 2 | 14,30 | 1 | 0 | 733 | 4 | − 7 | 44$\bar{1}$ | 15 | +15 |
| 82$\bar{3}$ | 4 | + 4 | 15,3$\bar{1}$ | 1 | − 1 | 833 | 6 | − 6 | 34$\bar{1}$ | 2 | + 3 |
| 72$\bar{3}$ | 7 | + 6 | 14,3$\bar{1}$ | 2 | − 2 | 10,33 | 2 | + 2 | 24$\bar{1}$ | 9 | + 8 |
| 62$\bar{3}$ | 4 | − 4 | 13,3$\bar{1}$ | 1 | + 1 | 11,33 | 2 | + 2 | 14$\bar{1}$ | 10 | +11 |
| 42$\bar{3}$ | 5 | − 6 | 12,3$\bar{1}$ | 1 | − 1 | 12,33 | 1 | − 1 | 041 | 4 | − 4 |
| 22$\bar{3}$ | 1 | + 3 | 11,3$\bar{1}$ | 3 | − 2 | 13,34$\bar{4}$ | 2 | − 1 | 141 | 17 | −17 |
| 12$\bar{3}$ | 8 | −12 | 10,3$\bar{1}$ | 5 | − 4 | 12,34$\bar{4}$ | 2 | − 2 | 241 | 1 | − 1 |
| 023 | 11 | − 8 | 93$\bar{1}$ | 3 | − 3 | 11,34$\bar{4}$ | 1 | 0 | 341 | 12 | −12 |
| 223 | 7 | − 6 | 83$\bar{1}$ | 4 | + 6 | 10,34$\bar{4}$ | 1 | + 1 | 441 | 10 | − 9 |
| 423 | 4 | + 4 | 73$\bar{1}$ | 8 | + 7 | 934$\bar{4}$ | 2 | − 3 | 541 | 7 | + 8 |
| 523 | 4 | + 4 | 63$\bar{1}$ | 11 | + 9 | 834$\bar{4}$ | 6 | + 5 | 641 | 12 | +10 |
| 723 | 8 | − 8 | 53$\bar{1}$ | 11 | +13 | 734$\bar{4}$ | 2 | − 2 | 741 | 5 | − 4 |
| 923 | 2 | − 1 | 43$\bar{1}$ | 31 | −29 | 534$\bar{4}$ | 5 | + 5 | 841 | 14 | +12 |
| 11,23 | 3 | + 2 | 33$\bar{1}$ | 3 | − 2 | 434$\bar{4}$ | 3 | + 4 | 941 | 10 | − 9 |
| 11,2$\bar{4}$ | 1 | − 2 | 23$\bar{1}$ | 17 | −20 | 334$\bar{4}$ | 2 | + 1 | 11,41 | 2 | − 1 |
| 10,2$\bar{4}$ | 1 | + 2 | 13$\bar{1}$ | 11 | −13 | 134$\bar{4}$ | 3 | − 4 | 13,41 | 1 | − 1 |
| 92$\bar{4}$ | 11 | + 6 | 031 | 2 | − 1 | 034 | 5 | + 5 | 14,41 | 1 | − 1 |
| 82$\bar{4}$ | 4 | − 3 | 131 | 1 | + 1 | 134 | 3 | − 3 | 13,4$\bar{5}$ | 2 | + 2 |
| 72$\bar{4}$ | 9 | + 7 | 231 | 15 | −14 | 334 | 4 | − 5 | 11,4$\bar{5}$ | 2 | − 2 |
| 62$\bar{4}$ | 10 | − 8 | 331 | 7 | − 7 | 434 | 5 | − 5 | 10,4$\bar{5}$ | 2 | + 2 |
| 42$\bar{4}$ | 6 | − 4 | 431 | 5 | − 4 | 534 | 4 | − 3 | 84$\bar{5}$ | 8 | + 7 |
| 024 | 3 | − 3 | 531 | 4 | − 5 | 634 | 8 | − 9 | 74$\bar{5}$ | 13 | +10 |
| 324 | 4 | + 4 | 631 | 1 | − 1 | 10,3$\bar{5}$ | 1 | + 1 | 64$\bar{5}$ | 7 | + 4 |
| 424 | 2 | − 1 | 731 | 9 | + 9 | 83$\bar{5}$ | 2 | + 1 | 54$\bar{5}$ | 4 | + 3 |
| 524 | 6 | − 5 | 831 | 12 | −11 | 73$\bar{5}$ | 1 | + 1 | 44$\bar{5}$ | 10 | +10 |
| 624 | 3 | − 2 | 931 | 4 | + 4 | 53$\bar{5}$ | 4 | + 1 | 24$\bar{5}$ | 6 | + 6 |
| 724 | 9 | − 8 | 10,31 | 2 | + 2 | 43$\bar{5}$ | 4 | + 4 | 14$\bar{5}$ | 5 | + 7 |
| 924 | 3 | + 2 | 12,31 | 4 | + 4 | 33$\bar{5}$ | 2 | + 1 | 042 | 2 | − 2 |
| 10,2$\bar{5}$ | 3 | − 3 | 14,31 | 1 | − 1 | 13$\bar{5}$ | 2 | + 3 | 142 | 6 | − 8 |
| 92$\bar{5}$ | 6 | + 6 | 13,3$\bar{2}$ | 2 | − 3 | 035 | 2 | 0 | 242 | 2 | − 2 |
| 82$\bar{5}$ | 6 | − 5 | 11,3$\bar{2}$ | 6 | − 5 | 235 | 2 | − 2 | 342 | 2 | + 2 |
| 32$\bar{5}$ | 4 | + 5 | 10,3$\bar{2}$ | 2 | + 1 | 335 | 2 | 0 | 442 | 2 | + 3 |
| 12$\bar{5}$ | 1 | 0 | 93$\bar{2}$ | 2 | + 2 | 435 | 3 | − 2 | 542 | 1 | − 1 |
| 025 | 6 | − 7 | 83$\bar{2}$ | 7 | + 6 | 535 | 2 | + 2 | 642 | 9 | +11 |
| 125 | 4 | + 3 | 73$\bar{2}$ | 4 | + 4 | 635 | 2 | − 2 | 742 | 14 | −14 |
| 225 | 4 | − 5 | 63$\bar{2}$ | 6 | − 8 | 935 | 1 | − 1 | 842 | 2 | + 1 |
| 425 | 3 | − 2 | 53$\bar{2}$ | 12 | −10 | 10,35 | 3 | − 3 | 942 | 3 | − 3 |
| 525 | 4 | − 4 | 43$\bar{2}$ | 21 | −21 | 73$\bar{6}$ | 1 | − 1 | 11,42 | 4 | + 3 |
| 10,2$\bar{6}$ | 2 | − 2 | 33$\bar{2}$ | 11 | −13 | 63$\bar{6}$ | 2 | + 2 | 12,42 | 3 | + 3 |
| 82$\bar{6}$ | 2 | − 2 | 23$\bar{2}$ | 4 | + 6 | 53$\bar{6}$ | 1 | + 1 | 13,42 | 2 | − 2 |
| 72$\bar{6}$ | 1 | − 2 | 13$\bar{2}$ | 5 | − 5 | 43$\bar{6}$ | 4 | + 4 | 54$\bar{3}$ | 8 | −10 |
| 52$\bar{6}$ | 4 | + 4 | 032 | 7 | − 7 | 33$\bar{6}$ | 3 | + 3 | 44$\bar{3}$ | 14 | +13 |
| 32$\bar{6}$ | 1 | + 1 | 132 | 13 | −11 | 13$\bar{6}$ | 2 | + 2 | 24$\bar{3}$ | 6 | + 4 |
| 22$\bar{6}$ | 5 | − 5 | 232 | 6 | − 6 | 036 | 2 | 0 | 14$\bar{3}$ | 4 | + 4 |
| 12$\bar{6}$ | 5 | − 4 | 332 | 11 | −13 | 336 | 2 | + 2 | 243 | 2 | + 2 |
| 026 | 5 | − 5 | 432 | 4 | + 4 | 436 | 1 | 0 | 343 | 2 | + 2 |
| 126 | 2 | + 2 | 532 | 1 | + 1 | 736 | 2 | − 2 | 543 | 6 | − 4 |
| 326 | 2 | + 2 | 632 | 4 | − 4 | 437 | 1 | + 1 | 544 | 3 | − 3 |
| 426 | 1 | + 1 | 732 | 1 | 0 | 337 | 2 | − 1 | 444 | 8 | + 7 |
| 826 | 1 | − 2 | 832 | 12 | − 8 | 137 | 1 | + 1 | 344 | 4 | + 4 |
| 52$\bar{7}$ | 2 | + 2 | 932 | 3 | − 5 | 040 | 7 | − 3 | 044 | 2 | + 3 |
| 42$\bar{7}$ | 1 | − 2 | 10,32 | 2 | + 3 | 140 | 4 | − 3 | 144 | 3 | + 5 |
| 32$\bar{7}$ | 1 | − 2 | 12,32 | 1 | 0 | 240 | 12 | +11 | 444 | 2 | − 2 |
| 22$\bar{7}$ | 2 | − 3 | 14,32 | 2 | − 2 | 340 | 19 | −16 | 54$\bar{5}$ | 2 | + 2 |
| 12$\bar{7}$ | 2 | − 2 | 13,3$\bar{3}$ | 4 | − 4 | 540 | 2 | − 1 | 34$\bar{5}$ | 1 | − 1 |

TABLE 5. (*Continued.*)

| *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $24\bar{5}$ | 2 | + 1 | $15\bar{4}$ | 3 | + 5 | 12,62 | 2 | − 2 | 573 | 3 | − 4 |
| $14\bar{5}$ | 2 | − 4 | 054 | 2 | − 2 | $46\bar{3}$ | 5 | − 5 | $57\bar{4}$ | 1 | − 1 |
| 045 | 5 | + 6 | 154 | 4 | + 5 | $26\bar{3}$ | 8 | − 8 | $47\bar{4}$ | 2 | − 2 |
| $44\bar{6}$ | 1 | + 1 | 354 | 2 | − 1 | $16\bar{3}$ | 5 | + 5 | $37\bar{4}$ | 1 | − 1 |
| $24\bar{6}$ | 5 | + 4 | 454 | 2 | + 2 | 263 | 3 | − 3 | $17\bar{4}$ | 1 | + 1 |
| $14\bar{6}$ | 2 | + 1 | 554 | 2 | + 1 | 363 | 5 | + 4 | 074 | 2 | − 1 |
| $04\bar{6}$ | 2 | + 3 | $55\bar{5}$ | 1 | + 2 | 463 | 14 | +10 | 174 | 2 | − 2 |
| 446 | 1 | − 1 | $15\bar{5}$ | 3 | + 3 | 563 | 3 | + 2 | 374 | 2 | − 4 |
| 546 | 1 | − 2 | 355 | 4 | − 5 | $56\bar{4}$ | 2 | − 2 | 574 | 2 | + 2 |
| 150 | 11 | −12 | 555 | 2 | − 2 | $46\bar{4}$ | 3 | − 2 | $57\bar{5}$ | 1 | − 1 |
| 250 | 5 | + 7 | $55\bar{6}$ | 1 | 0 | $16\bar{4}$ | 3 | + 2 | $37\bar{5}$ | 2 | − 2 |
| 350 | 1 | + 1 | $45\bar{6}$ | 1 | − 1 | 064 | 2 | + 2 | $27\bar{5}$ | 1 | + 1 |
| 450 | 3 | + 1 | $35\bar{6}$ | 1 | − 1 | 264 | 5 | − 5 | 375 | 1 | + 1 |
| 550 | 2 | − 2 | $25\bar{6}$ | 1 | + 1 | 464 | 4 | − 2 | 475 | 2 | − 2 |
| 650 | 2 | 0 | $15\bar{6}$ | 1 | + 2 | $56\bar{5}$ | 2 | − 3 | 180 | 3 | − 5 |
| 750 | 8 | + 6 | 356 | 1 | − 2 | $37\bar{5}$ | 1 | + 1 | 380 | 1 | − 2 |
| 950 | 3 | + 2 | 060 | 10 | − 9 | $26\bar{5}$ | 1 | 0 | 580 | 1 | + 1 |
| 10,50 | 1 | + 2 | 160 | 2 | + 3 | $16\bar{5}$ | 3 | + 4 | 680 | 2 | − 3 |
| 11,50 | 2 | − 2 | 360 | 10 | + 9 | 265 | 2 | − 2 | 880 | 2 | − 2 |
| 12,50 | 1 | + 1 | 460 | 3 | + 3 | 465 | 1 | + 1 | 10,8$\bar{1}$ | 1 | + 1 |
| 13,50 | 1 | − 2 | 560 | 6 | + 4 | 170 | 2 | 0 | 98$\bar{1}$ | 1 | 0 |
| 12,5$\bar{1}$ | 2 | + 2 | 660 | 2 | + 2 | 270 | 3 | − 3 | 88$\bar{1}$ | 3 | − 2 |
| 11,5$\bar{1}$ | 1 | + 1 | 10,60 | 2 | − 2 | 370 | 1 | + 2 | 78$\bar{1}$ | 3 | − 2 |
| 10,5$\bar{1}$ | 1 | − 1 | 11,60 | 1 | − 1 | 470 | 4 | + 5 | 68$\bar{1}$ | 3 | − 2 |
| 95$\bar{1}$ | 6 | + 4 | 12,60 | 1 | + 2 | 570 | 2 | − 3 | 58$\bar{1}$ | 1 | − 2 |
| 85$\bar{1}$ | 6 | − 6 | 12,6$\bar{1}$ | 1 | − 1 | 770 | 5 | − 4 | 28$\bar{1}$ | 2 | + 1 |
| 75$\bar{1}$ | 1 | + 1 | 11,6$\bar{1}$ | 1 | − 1 | 870 | 1 | − 1 | 18$\bar{1}$ | 2 | + 3 |
| 55$\bar{1}$ | 2 | − 4 | 10,6$\bar{1}$ | 3 | − 1 | 970 | 3 | − 3 | 081 | 2 | + 2 |
| 45$\bar{1}$ | 7 | + 7 | 96$\bar{1}$ | 1 | − 1 | 10,70 | 3 | − 3 | 181 | 3 | − 4 |
| 35$\bar{1}$ | 7 | + 6 | 86$\bar{1}$ | 1 | + 1 | 11,7$\bar{1}$ | 2 | − 2 | 281 | 3 | + 3 |
| 25$\bar{1}$ | 3 | + 1 | 76$\bar{1}$ | 2 | − 1 | 10,7$\bar{1}$ | 1 | − 1 | 381 | 5 | + 5 |
| 15$\bar{1}$ | 8 | − 7 | 66$\bar{1}$ | 1 | − 2 | 97$\bar{1}$ | 3 | − 2 | 481 | 1 | + 1 |
| 051 | 8 | + 7 | 56$\bar{1}$ | 5 | + 5 | 77$\bar{1}$ | 3 | − 2 | 581 | 1 | + 1 |
| 251 | 2 | + 2 | 46$\bar{1}$ | 3 | + 2 | 67$\bar{1}$ | 2 | + 2 | 681 | 2 | − 2 |
| 351 | 2 | + 3 | 36$\bar{1}$ | 2 | + 1 | 47$\bar{1}$ | 4 | + 3 | $88\bar{2}$ | 1 | − 1 |
| 451 | 10 | + 6 | 26$\bar{1}$ | 3 | − 2 | 37$\bar{1}$ | 2 | + 3 | $78\bar{2}$ | 3 | − 3 |
| 651 | 7 | + 8 | 16$\bar{1}$ | 8 | − 7 | 27$\bar{1}$ | 3 | + 2 | $48\bar{2}$ | 3 | + 3 |
| 751 | 6 | + 3 | 061 | 12 | −10 | 17$\bar{1}$ | 6 | − 6 | $38\bar{2}$ | 1 | + 1 |
| 10,51 | 2 | + 1 | 161 | 3 | + 3 | 071 | 10 | − 9 | $28\bar{2}$ | 2 | + 2 |
| 12,51 | 2 | + 2 | 261 | 2 | + 4 | 171 | 4 | − 4 | $18\bar{2}$ | 1 | + 1 |
| 13,5$\bar{2}$ | 1 | + 2 | 361 | 5 | + 4 | 271 | 3 | − 2 | 082 | 4 | + 3 |
| 10,5$\bar{2}$ | 5 | − 5 | 461 | 2 | + 2 | 371 | 2 | + 2 | 182 | 2 | + 2 |
| $95\bar{2}$ | 1 | + 1 | 561 | 3 | + 2 | 471 | 4 | + 3 | 282 | 4 | + 4 |
| $85\bar{2}$ | 2 | − 1 | 661 | 4 | − 3 | 571 | 3 | − 2 | 382 | 2 | + 2 |
| $75\bar{2}$ | 3 | 0 | 761 | 1 | + 2 | 671 | 2 | − 3 | 482 | 2 | + 2 |
| $65\bar{2}$ | 8 | + 7 | 861 | 3 | − 3 | 771 | 4 | − 3 | 583 | 2 | − 3 |
| $55\bar{2}$ | 9 | + 9 | 961 | 3 | + 2 | 871 | 2 | − 2 | 882 | 1 | + 1 |
| $35\bar{2}$ | 12 | +14 | 10,61 | 2 | + 1 | 10,71 | 3 | − 3 | 982 | 1 | − 1 |
| $25\bar{2}$ | 6 | − 7 | 11,61 | 1 | + 1 | 11,71 | 2 | + 2 | $58\bar{3}$ | 1 | + 1 |
| $15\bar{2}$ | 1 | − 1 | 12,61 | 2 | + 2 | $97\bar{2}$ | 1 | − 1 | $48\bar{3}$ | 2 | + 1 |
| 152 | 3 | + 3 | 12,6$\bar{2}$ | 1 | − 1 | $87\bar{2}$ | 1 | − 1 | 083 | 3 | + 3 |
| 252 | 3 | + 2 | 10,6$\bar{2}$ | 3 | − 3 | $77\bar{2}$ | 1 | − 1 | 183 | 2 | − 2 |
| 452 | 9 | + 9 | $96\bar{3}$ | 3 | − 3 | $47\bar{3}$ | 3 | + 3 | 283 | 3 | + 5 |
| 552 | 1 | − 1 | $86\bar{3}$ | 3 | − 3 | $37\bar{3}$ | 5 | − 5 | 383 | 2 | − 2 |
| 652 | 2 | + 2 | $76\bar{3}$ | 2 | − 2 | $27\bar{3}$ | 4 | + 4 | 483 | 3 | + 3 |
| 752 | 5 | + 5 | $66\bar{3}$ | 2 | − 2 | $17\bar{3}$ | 7 | − 8 | $48\bar{4}$ | 1 | − 1 |
| 852 | 2 | + 1 | $56\bar{3}$ | 1 | 0 | 072 | 7 | − 7 | $38\bar{4}$ | 1 | + 1 |
| 952 | 2 | + 3 | $36\bar{3}$ | 3 | − 3 | 172 | 4 | + 5 | $18\bar{4}$ | 3 | + 4 |
| 10,52 | 6 | + 4 | $26\bar{3}$ | 10 | −11 | 372 | 2 | + 4 | 084 | 1 | + 2 |
| 11,52 | 3 | + 3 | $16\bar{3}$ | 2 | + 2 | 472 | 2 | − 1 | 284 | 2 | + 2 |
| $55\bar{3}$ | 9 | +11 | 062 | 7 | − 6 | 572 | 5 | − 4 | 484 | 3 | + 1 |
| $45\bar{3}$ | 5 | − 6 | 162 | 5 | − 5 | 672 | 1 | − 2 | 190 | 4 | + 2 |
| $35\bar{3}$ | 4 | + 4 | 262 | 2 | + 4 | 772 | 1 | − 2 | 290 | 1 | 0 |
| $25\bar{3}$ | 2 | + 2 | 362 | 4 | − 4 | 872 | 1 | − 1 | 390 | 4 | + 3 |
| $15\bar{3}$ | 2 | − 2 | 462 | 9 | − 8 | 972 | 1 | 0 | 490 | 1 | + 1 |
| 053 | 6 | − 7 | 562 | 5 | + 5 | 10,72 | 4 | − 4 | 590 | 2 | + 3 |
| 153 | 3 | + 4 | 662 | 6 | − 6 | $57\bar{3}$ | 2 | − 2 | 690 | 1 | − 2 |
| 453 | 2 | + 2 | 762 | 5 | + 5 | $37\bar{3}$ | 4 | − 5 | 79$\bar{1}$ | 1 | − 1 |
| 553 | 2 | + 4 | 862 | 1 | + 1 | 073 | 3 | − 3 | 69$\bar{1}$ | 1 | − 1 |
| $55\bar{4}$ | 3 | + 3 | 962 | 4 | + 3 | 173 | 4 | + 5 | 59$\bar{1}$ | 2 | + 1 |
| $25\bar{4}$ | 4 | + 4 | 10,62 | 2 | + 2 | 373 | 4 | − 4 | 39$\bar{1}$ | 1 | 0 |

TABLE 5. (*Continued.*)

| *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) | *hkl* | F (exp.) | F (calc.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $29\bar{1}$ | 2 | − 2 | $69\bar{2}$ | 1 | − 1 | 592 | 1 | + 1 | 2,10,$\bar{1}$ | 2 | − 2 |
| $19\bar{1}$ | 4 | + 3 | $39\bar{2}$ | 1 | + 1 | 692 | 1 | + 1 | 1,10,$\bar{1}$ | 1 | − 2 |
| 091 | 2 | + 2 | $29\bar{3}$ | 2 | − 2 | $59\bar{3}$ | 1 | + 1 | 1,10,1 | 1 | + 2 |
| 191 | 6 | + 5 | $19\bar{2}$ | 2 | + 3 | 393 | 3 | + 4 | 3,10,1 | 2 | − 3 |
| 291 | 4 | + 3 | 092 | 2 | + 2 | 1,10,0 | 1 | + 2 | 5,10,1 | 3 | − 4 |
| 391 | 4 | + 3 | 192 | 1 | 0 | 3,10,0 | 1 | + 2 | 4,10,$\bar{3}$ | 3 | − 3 |
| 591 | 1 | + 1 | 292 | 2 | + 1 | 5,10,0 | 2 | − 2 | 2,10,$\bar{5}$ | 1 | − 1 |
| 691 | 2 | − 2 | 392 | 1 | 0 | 5,10,$\bar{1}$ | 1 | + 1 | 1,10,$\bar{2}$ | 1 | − 1 |
| 891 | 2 | + 3 | 492 | 1 | − 1 | 3,10,$\bar{1}$ | 1 | + 2 | 3,10,2 | 3 | − 3 |
| $79\bar{3}$ | 1 | − 1 | | | | | | | | | |

*X*-Ray rotation photographs were taken with the crystals mounted successively about the three principal axes and [101] to determine the cell dimensions, which were obtained by measurement of the layer lines: $a = 12{\cdot}22$, $b = 8{\cdot}28$, $c = 5{\cdot}82$ Å, and $\beta = 93° 18'$. The density, 1·178, determined by flotation in sodium iodide solution, agreed well with that calculated (1·176) for two molecules of $C_{16}H_{16}$ per unit cell. Intensity data were obtained by means of Weissenberg moving-film photographs about *a*, *b*, and *c*, for the zero and several layers by the equi-inclination method up to a limit of $\mu = 20°$. Multiple films were used in the usual ways, and the intensities were estimated visually by comparison with a calibrated film strip. Some 1200 different planes gave reflexions which were observed; the structure amplitudes for each were calculated from the intensities by applying the usual corrections, and they were placed on the absolute scale by Wilson's statistical method. A few reflexions were lost by the geometrical limitations of the Weissenberg camera, but on account of the high temperature factor ($B = 5{\cdot}0 \times 10^{-16}$ Å$^2$) the numerical values of these F's would be expected to be small, and no attempt was made to correct for their absence.

All the Fourier syntheses were computed manually by means of Beevers–Lipson strips, the *x* and *y* values being summed at intervals of 1/120ths of the cell edge, and *z* at 1/60ths. The structure amplitudes were also computed manually, and the final set were used to construct an experimental atomic scattering curve having the following values for $f_e$:

| $(\sin\theta)/\lambda$ ..... | 0 | 0·1 | 0·2 | 0·3 | 0·4 | 0·5 | 0·6 |
|---|---|---|---|---|---|---|---|
| $f_e$ ..... | 6·00 | 4·72 | 2·95 | 1·62 | 0·85 | 0·48 | 0·32 |

No account was taken of the hydrogen atoms. The agreement between the calculated and the experimental values of the structure-amplitudes is shown in Table 5. About 300 planes with unobserved intensities have been omitted from this Table; all of these gave very small values for F(calc.). The discrepancy as given by the usual residual *R* is 0·123 for the $\{h0l\}$, and 0·163 for all the $\{hkl\}$ terms.

The author thanks Professor W. Baker for suggesting this topic, and for the samples of di-*m*-xylylene.

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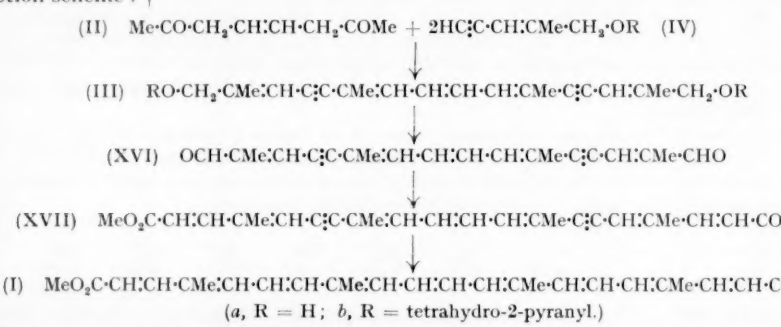
**651.** *Carotenoids and Related Compounds. Part I. Total Synthesis of "all-trans"-Methylbixin and of a Diketone with the Capsorubin Chromophore.*

By Rashid Ahmad and B. C. L. Weedon.

Direct total syntheses of the two compounds mentioned in the title are described.

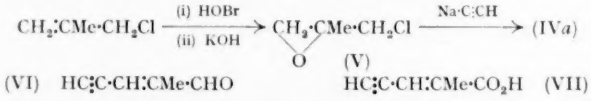
Within the last few years syntheses of β-carotene, lycopene, and some related hydrocarbons have been reported by the Karrer and the Inhoffen school (for summaries see *Ann. Reports*, 1950 and 1951; Inhoffen and Siemer, *Fortschritte der Chemie organischer Naturstoffe*, 1952, **9**, 1). The present series of papers will describe investigations undertaken primarily to develop routes to the many important natural carotenoids, and derived compounds, which in addition to a chain of conjugated double bonds possess two or more functional groups (cf., Karrer and Jucker, "Carotinoide," Birkhäuser et Cie. A-G., Basel, 1948; Goodwin, "The Comparative Biochemistry of the Carotenoids," Chapman and Hall Ltd., London, 1952). This communication deals mainly with a new and direct total synthesis of "all-*trans*"-methylbixin (I) * by the route indicated in the following reaction scheme : †




(*a*, R = H; *b*, R = tetrahydro-2-pyranyl.)

A formal synthesis of (I), by degradation of natural lycopene, was described earlier by Kuhn and Grundmann (*Ber.*, 1932, **65**, 1880).

Recently a convenient preparation of oct-4-ene-2 : 7-dione (II), which possesses a carbon skeleton identical with that of the central portion of most carotenoids, was reported (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089). To extend the chain of this diketone in both directions to give a $C_{20}$ intermediate (III*a*), with a polyisoprenoid structure, a condensation with 2-methylpent-2-en-4-yn-1-ol (IV*a*) was envisaged. This hitherto unknown alcohol was prepared from β-methylepichlorohydrin (V) (Hurd and Winberg, *J. Amer. Chem. Soc.*, 1951, **73**, 917) by adapting the reaction discovered by




Haynes, Heilbron, Jones, and Sondheimer (*J.*, 1946, 1584) with epichlorohydrin. Treatment of (V) with sodium acetylide in liquid ammonia furnished (35%) the alcohol (IV*a*) directly. It exhibited the expected light-absorption properties, and on catalytic hydrogenation gave the known 2-methylpentan-1-ol. Oxidation of the alcohol (IV*a*), in acetone,

* Note on nomenclature (cf. Escue and Zechmeister, *J. Amer. Chem. Soc.*, 1944, **66**, 322) : Bixin, the natural carotenoid from the seeds of the Annato tree (*Bixa orellana* L.), is a methyl hydrogen ester of the nonaenedicarboxylic acid "norbixin"; the corresponding diester is termed "methylbixin." Irradiation (in the presence of iodine) of natural bixin and methylbixin, both of which contain one double bond in the *cis*-configuration, gives the "all-*trans*"-isomers.

† A preliminary account of this work was given in *Chem. and Ind.*, 1952, 882.

with manganese dioxide (cf. Bharucha and Weedon, *J.*, 1953, 1584) yielded the aldehyde (VI), whilst with chromic acid (cf. Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586) the crystalline acid (VII) was formed (55%).

Unpromising results were obtained in attempts to cause the Grignard reagent from methylpentenynol (IV*a*) to react with ketones. However, with acetone, the lithium derivative of its tetrahydro-2-pyranyl ether (IV*b*) (cf. Parham and Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 4187) gave the alcohol (VIII) in 80% yield. [Similarly (IX) was prepared (65%) from 3-tetrahydro-2′-pyranyloxyprop-1-yne (Henbest, Jones, and Walls, *J.*, 1950, 3646) and acetaldehyde.] This procedure seemed suitable for use with the $C_8$ diketone (II), but a method was now required for regenerating polyene glycols from their bistetrahydropyranyl ethers under mild conditions. Experiments with the bis-ether (X), prepared by oxidative coupling of the tetrahydropyranyl ether of pent-2-en-

(VIII) HO·CMe$_2$·C:C·CH:CMe·CH$_2$·OR HO·CHMe·C:C·CH$_2$·OR (IX)

(X) (·C:C·CH:CH·CH$_2$·OR)$_2$ (R = tetrahydro-2-pyranyl)

4-yn-1-ol in the presence of cuprous ammonium chloride, showed that this could be achieved almost quantitatively by treatment with alcohol containing catalytic amounts of toluene-*p*-sulphonic acid. While this work was in hand a very similar process was reported (Dauben and Bradlow, *J. Amer. Chem. Soc.*, 1952, **74**, 559) for the regeneration of cholesterol from its tetrahydropyranyl ether.

As a readily available model substance with which to develop methods for transformations which it was proposed to carry out with the $C_{20}$ intermediate (III*a*), the $C_{10}$ glycol (XI) was prepared (70%) by oxidative coupling of the methylpentenynol (IV*a*). Similar oxidation of the corresponding acid (VII) gave the dicarboxylic acid (XII) in 80% yield.

(XI) (·C:C·CH:CMe·CH$_2$·OH)$_2$ (·C:C·CH:CMe·CO$_2$H)$_2$ (XII)

(XIII) (·C:C·CH:CMe·CHO)$_2$ (·C:C·CH:CMe·CH:CH·CO$_2$Me)$_2$ (XIV)

(XV) (·C:C·CH:CMe·CH:CH·COMe)$_2$

Oxidation of the $C_{10}$ glycol (XI) in acetone with manganese dioxide (cf. Ahmad *et al.*, *loc. cit.*) gave (85%) the dialdehyde (XIII) which, by condensation with malonic acid followed by esterification, was converted into the diester (XIV) in 5% overall yield. It is noteworthy that in this Doebner reaction, and in those described below and in Part III (*J.*, 1953, 3299), the alkylidenemalonic acids formed initially, unlike those from polyene monoaldehydes containing four or more double bonds (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1318), were decarboxylated spontaneously under the conditions of the reaction. Condensation of the dialdehyde (XIII) with acetone in the presence of aluminium *tert.*-butoxide furnished the diketone (XV) in 40% yield.

Reaction of the lithium derivative of the tetrahydropyranyl ether (IV*b*) with the $C_8$ diketone (II), and dehydration of the initial product, gave the crystalline diether (III*b*) in 8% overall yield. This on treatment with alcoholic toluene-*p*-sulphonic acid afforded (90%) the $C_{20}$ glycol (III*a*), possessing the same carbon skeleton as crocetin. When the glycol (III*a*) was shaken in acetone with manganese dioxide the dialdehyde (XVI) was produced in almost quantitative yield. Condensation of (XVI) with malonic acid, and esterification of the resulting diacid, furnished the diester (XVII) in 20% overall yield. Partial reduction of (XVII) over a lead-poisoned palladium catalyst (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) gave "all-*trans*"-methylbixin (I), identical in all respects with an authentic specimen prepared from methyl-(natural-)bixin (for which the authors are greatly indebted to Prof. L. Zechmeister). It is very probable that in this partial hydrogenation an unstable intermediate was formed initially, and subsequently rearranged to "all-*trans*"-methylbixin; after removal of the latter from the reaction product, irradiation of the residue in the presence of a trace of iodine gave a further small amount of "all-*trans*"-methylbixin (total yield 10%).

Condensation of the dialdehyde (XVI) with pinacolone yielded (45%) the diketone (XVIII*a*) which, by partial reduction, was converted (5%) into the polyene (XIX*a*). The latter possesses the same chromophore as capsorubin, a carotenoid from paprika to which

Zechmeister and Cholnoky (*Annalen*, 1934, **509**, 269; 1935, **516**, 30) assigned the provisional structure (XIX*b*), and β-carotenone (XIX*c*), an oxidation product of β-carotene (Kuhn and Brockmann, *Annalen*, 1935, **516**, 123).

$$R{\cdot}CMe_2{\cdot}CO{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}C{\equiv}C{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}C{\equiv}C{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}CO{\cdot}CMe_2{\cdot}R$$
(XVIII)

$$R{\cdot}CMe_2{\cdot}CO{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}CO{\cdot}CMe_2{\cdot}R$$
(XIX)

[*a*, R = Me; *b*, R = $CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2Me$; *c*, R = $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COMe$.]

All the fully conjugated polyenes reported above were isolated as crystalline solids. As expected, the ultra-violet light-absorption properties, given in Table 1, of the methylpentenynol (IV*a*), the $C_{10}$ glycol (XI), and related substances, are very similar to those of

TABLE 1.

| | Methylpentenynol series (R = Me) | | Pentenynol series (R = H) | |
|---|---|---|---|---|
| | ($\lambda_{max.}$ mμ) | $\varepsilon_{max.}$ | $\lambda_{max.}$ (mμ) | $\varepsilon_{max.}$ |
| $HC{\equiv}C{\cdot}CH{:}CR{\cdot}CH_2{\cdot}OH$ | 226 | 14,500 | 223 [1] | 15,000 |
| | | | 229 * | 10,000 |
| $HC{\equiv}C{\cdot}CH{:}CR{\cdot}CH_2{\cdot}OTp$ § | 227 | 15,000 | 218 } 223 } | 16,500 |
| $HC{\equiv}C{\cdot}CH{:}CR{\cdot}CHO$ | 251 ‡ | 15,000 | — | — |
| | 256 | 18,000 | — | — |
| | 264 | 18,000 | (261 [2] | 12,500) |
| $HC{\equiv}C{\cdot}CH{:}CR{\cdot}CO_2H$ | 247 } 251 } | 18,000 | 242 [3] | 12,500 |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CH_2{\cdot}OH)_2$ | — | — | 233 [3] | 38,000 |
| | 242 | 33,500 | 237 | 39,000 |
| | 251 | 30,000 | 247 | 30,000 |
| | 267 | 10,000 | 262 | 12,000 |
| | 280 | 17,500 | 276 | 20,000 |
| | 298 | 22,000 | 293 | 30,000 |
| | 320 | 17,500 | 312 | 23,000 |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CH_2{\cdot}OTp)_2$ | — | — | 227 | 38,000 |
| | | | 237 | 31,000 |
| | | | 248 | 22,000 |
| | | | 278 | 15,000 |
| | | | 294 | 22,000 |
| | | | 313 | 18,000 |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CHO)_2$ | — | — | 251 † [4] | 12,500 |
| | 286 | 24,500 | 270 | 23,500 |
| | 289 | 24,500 | 280 | 27,000 |
| | 314 | 20,500 | 310 | 20,000 |
| | 332 | 28,500 | 330 | 25,500 |
| | 356 | 24,500 | 353 | 23,500 |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CO_2Me)_2$ | — | — | 219 [3] | 26,000 |
| | 258 | 25,000 | 258 | 27,500 |
| | 268 | 25,000 | 268 | 27,500 |
| | 280 | 24,000 | — | — |
| | 304 | 21,000 | 297 | 17,500 |
| | 325 | 27,000 | 316 | 28,500 |
| | 347 | 25,500 | 339 | 27,500 |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CH{:}CH{\cdot}CO_2Me)_2$ | 346 † | 37,500 | — | — |
| | 370 | 48,000 | | |
| | 399 | 43,500 | | |
| $(\cdot C{\equiv}C{\cdot}CH{:}CR{\cdot}CH{:}CH{\cdot}COMe)_2$ | 328 ‡ | 30,000 | — | — |
| | 348 | 35,000 | | |
| | 369 | 39,500 | | |
| | 402 | 35,000 | | |

* Inflexion. † In chloroform. ‡ In hexane. § Tp = tetrahydro-2-pyranyl.

[1] Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583. [2] 3-Methylpent-2-en-4-ynal, Jones and Weedon, *J.*, 1946, 939. [3] Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586. [4] Weedon, unpublished result.

the corresponding compounds from pent-2-en-4-yn-1-ol. The absorption data for the $C_{20}$ glycol (III*a*), and derived compounds, are given in Table 2. The differences between the spectra of " all-*trans* "-methylbixin (I), the polyene diketone (XIX*a*), and those of

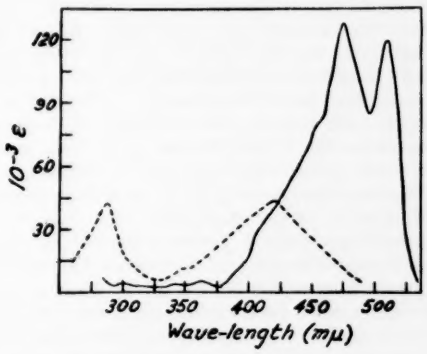
their diacetylenic analogues (XVII) and (XVIII*a*), are striking; both $\lambda_{max.}$ and $\epsilon_{max.}$ are markedly reduced in the latter pair (see also Figure). Previously it has been found that substitution of one double bond in a polyene hydrocarbon by a triple bond results in a

TABLE 2.

| | $\lambda_{max.}$ (mμ) | ε | Solvent | | $\lambda_{max.}$ (mμ) | ε | Solvent |
|---|---|---|---|---|---|---|---|
| Bisether (III*b*) | 367 | 55,500 | *cyclo*-Hexane | Dialdehyde (XVI) | 400 | 45,000 | EtOH |
| | | | | Diketone (XVIII*a*) | 296 | 37,000 | $CHCl_3$ |
| Glycol (III*a*) | 353 | 42,500 | EtOH | | 418 | 37,000 | |
| | 364 | 48,500 | | | 435 | 38,500 | |
| Diester (XVII) | 284 | 44,000 | $CHCl_3$ | Polyene diketone (XIX*a*) | 485 | 105,000 | $C_6H_6$ |
| | 420 | 44,000 | | | 518 | 90,000 | |
| " all-*trans* "-(I), synthetic | 475 | 125,000 | $C_6H_6$ | Capsorubin (XIX*b*) [1] | 486 | — | $C_6H_6$ |
| | 507 | 118,000 | | | 520 | — | |
| " all-*trans* "-(I), authentic | 475 | 128,000 | $C_6H_6$ | β-Carotenone (XIX*c*) [2] | 486 | — | $C_6H_6$ |
| | 507 | 120,000 | | | 522 | — | |

[1] Zechmeister and Cholnoky, *Annalen*, 1934, **509**, 269. [2] Kuhn and Brockmann, *ibid.*, 1935, **516**, 123.

displacement of the main maximum by 10—20 mμ to shorter wave-lengths (Inhoffen, Pommer, and Meth, *Annalen*, 1949, **565**, 45; Inhoffen, Bohlmann, and Rummert, *ibid.*, 1950, **569**, 226; Inhoffen, Bohlmann, Bartram, Pommer, and Rummert, *ibid.*, 1950, **570**, 54), whilst with two adjacent triple bonds in a polyene chain shifts of up to 36 mμ have




——— " all-*trans* "-Methylbixin.
– – – – – Diacetylenic analogue.

been observed (Bohlmann, *Chem. Ber.*, 1951, **84**, 545; Inhoffen, Bohlmann, Aldag, Bork, and Leibner, *Annalen*, 1951, **573**, 1). In the present examples, in which the two triple bonds are separated, the maximum in the visible region is shifted to an even greater extent (50—55 mμ), and a high-intensity partial chromophore band, reminiscent of a " *cis*-peak " (cf. Zechmeister, *Chem. Reviews*, 1944, **34**, 267), is produced in the ultra-violet region. Similar effects are apparent in the recently published spectrum of the hydrocarbon (XX) (Garbers, Eugster, and Karrer, *Helv. Chim. Acta*, 1952, **35**, 1850).

(XX) Ph·CH:CH·CMe:CH·C:C·CMe:CH·CH:CH·CH:CMe·C:C·CH:CMe·CH:CHPh

The extension of the routes described above to the synthesis of other carotenoids is now being examined.

## EXPERIMENTAL

Whenever possible, operations were carried out in an atmosphere of pure nitrogen. Solutions of polyenes were evaporated under reduced pressure.

Light-absorption data were determined in alcohol unless stated otherwise.

Chromatography was on alumina, pretreated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 3120), and graded (Brockmann and Schodder, *Ber.*, 1941, **74**, 73).

*2-Methylpent-2-en-4-yn-1-ol* (IV*a*).—A solution of β-methylepichlorohydrin (95 g.) (Hurd

and Winberg, *J. Amer. Chem. Soc.*, 1951, **73**, 917) in ether (200 c.c.) was added during 1½ hr. to a stirred solution of sodium acetylide (from 48 g. of sodium; cf. Heilbron, Jones, and Weedon, *J.*, 1945, 83) in liquid ammonia (2 l.). After the mixture had been stirred for 15 hr., ammonium chloride (125 g.) was added to decompose the complex, and the ammonia was allowed to evaporate. Isolation of the product from the residue with ether gave the *alcohol* (33 g.), b. p. 85—87°/20 mm., $n_D^{20}$ 1·4890 (Found: C, 74·5; H, 8·5. $C_6H_8O$ requires C, 75·0; H, 8·4%). Light absorption: see Table 1. The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 104° (Found: C, 76·85; H, 5·85. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·65%).

2-*Methylpentan*-1-*ol*.—The preceding alcohol (1·0 g.) in methanol (5 c.c.) was shaken in hydrogen in the presence of a platinum catalyst (Adams; 50 mg.) until absorption was complete (754 c.c. at 20°/757 mm., equiv. to 2·9 double bonds). Removal of catalyst and solvent, and distillation of the residue, gave 2-methylpentan-1-ol (0·5 g.), b. p. 145—147°, $n_D^{21}$ 1·4171. The α-naphthylurethane crystallised from light petroleum as needles, m. p. 75—77°, undepressed on admixture with an authentic specimen and with that described by Heilbron, Jones, McCombie, and Weedon (*J.*, 1945, 84).

2-*Methylpent*-2-*en*-4-*yn*-1-*al* (VI).—A solution of 2-methylpent-2-en-4-yn-1-ol (2·5 g.) in acetone (100 c.c.) was shaken with manganese dioxide (20 g.) for 24 hr. Removal of oxide and solvent, and distillation of the residue, gave the aldehyde as an unstable liquid (0·9 g.), b. p. 48—49°/24 mm. Light absorption: see Table 1. The *semicarbazone* crystallised from alcohol as plates which decomposed at *ca.* 125° without melting (Found: N, 27·65. $C_7H_9ON_3$ requires N, 27·8%). Light absorption: Max., 292 mμ; ε = 28,500. Inflexions, 284 and 298 mμ; ε = 25,500. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as prisms, m. p. 163° (decomp.; bath preheated to 155°) (Found: C, 52·5; H, 3·95. $C_{12}H_{10}O_4N_4$ requires C, 52·6; H, 3·7%). Light absorption in $CHCl_3$: Max. (main band only), 378 mμ; ε = 33,500.

2-*Methylpent*-2-*en*-4-*ynoic Acid* (VII).—An aqueous solution (25 c.c.) of chromium trioxide (4·8 g.) and concentrated sulphuric acid (8 g.) was added during 20 min. to a cooled (10°) solution of 2-methylpent-2-en-4-yn-1-ol (2·5 g.) in acetone (15 c.c.). The mixture was stirred at 20° for 2 hr. and then poured into water and extracted thoroughly with ether. The extract was concentrated (to *ca.* 100 c.c.) and washed repeatedly with saturated aqueous sodium hydrogen carbonate. The alkaline extract was acidified and the product isolated with ether, giving a solid (1·8 g.), m. p. 68—71°. Crystallisation from light petroleum (b. p. 40—60°) yielded the *acid* as needles, m. p. 72—73° (Found: C, 65·7; H, 5·75. $C_6H_6O_2$ requires C, 65·5; H, 5·45%). Light absorption: see Table 1.

2-*Methyl*-1-*tetrahydro*-2′-*pyranyloxypent*-2-*en*-4-*yne* (IV*b*) (cf. Henbest, Jones, and Walls, *J.*, 1950, 3646).—Phosphorus oxychloride (50 mg.) was added to a cooled (ice-bath) solution of 2-methylpent-2-en-4-yn-1-ol (6·0 g.) in dihydropyran (5·4 g.; freshly distilled). When the vigorous exothermic reaction had subsided, the mixture was kept at 20° for 3 hr. and then diluted with ether. The ethereal solution was washed with aqueous potassium hydroxide (10% w/v), then with water, dried ($Na_2SO_4$), and evaporated. Distillation of the residue gave the *tetrahydropyranyl ether* (9·2 g.), b. p. 68—69°/0·1 mm., $n_D^{22}$ 1·4880 (Found: C, 73·1; H, 9·25. $C_{11}H_{14}O_2$ requires C, 73·35; H, 8·9%). Light absorption: see Table 1.

2 : 6-*Dimethyl*-7-*tetrahydro*-2′-*pyranyloxyhept*-5-*en*-3-*yn*-2-*ol* (VIII).—A solution of phenyl-lithium (from 0·5 g. of lithium) in ether (50 c.c.) was added dropwise to a cooled (0°) solution of the preceding tetrahydropyranyl ether (6·1 g.) in ether (60 c.c.). After the mixture had been stirred at 0° for 7 hr., acetone (2·0 g.) in ether (25 c.c.) was added (15 min.) and the temperature of the mixture was allowed to rise to 20° over a period of 8 hr. The mixture was then boiled for 10 min. and again cooled. Decomposition of the complex with a saturated solution of ammonium chloride, and isolation of the product in the usual way, gave the *alcohol* (6·3 g.), b. p. 70—80° (bath-temp.)/$10^{-4}$ mm., $n_D^{23}$ 1·4991 [Found: C, 70·35; H, 9·25%; active H (Zerewitinoff), 1·1 atoms. $C_{14}H_{22}O_3$ requires C, 70·55; H, 9·25%]. Light absorption: Max., 227 mμ; ε = 14,500. Inflexion, 234 mμ; ε = 12,000.

When the preceding reaction was carried out with the Grignard complex of the tetrahydropyranyl ether in either ether or tetrahydrofuran solution the required alcohol was isolated in only 30 and 25% yield respectively (50 and 65% based on unrecovered starting material).

5-*Tetrahydro*-2′-*pyranyloxypent*-3-*yn*-2-*ol* (IX).—An ethereal solution of phenyl-lithium (from 1·2 g. of lithium) was added to 3-tetrahydro-2′-pyranyloxyprop-1-yne (12·2 g.) (*idem*, *loc. cit.*), in ether (100 c.c.), and the mixture was stirred at 0° for 8 hr. Acetaldehyde (5·0 g.; *ca.* 20% excess) in ether (25 c.c.) was added dropwise and the temperature of the mixture was then allowed to rise to 20° during 8 hr. Isolation of the product in the usual way gave the

*alcohol* (10·5 g.), b. p. 83—85°/$10^{-3}$ mm., $n_D^{22}$ 1·4761 (Found: C, 65·25; H, 8·8. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%).

*5-Tetrahydro-2'-pyranyloxypent-3-en-2-ol.*—The preceding tetrahydropyranyl ether (5·5 g.) in ethyl acetate (15 c.c.) was shaken with a lead-poisoned palladium on calcium carbonate catalyst (1·0 g.) (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) until 1 mol. had been absorbed (800 c.c. at 19°/775 mm.). Removal of catalyst and solvent gave the *alcohol* (4·9 g.), b. p. 75—80° (bath-temp.)/$10^{-4}$ mm., $n_D^{22}$ 1·4710 (Found: C, 64·4; H, 9·75. $C_{10}H_{18}O_3$ requires C, 64·45; H, 9·75%).

1 : 10-*Bistetrahydro-2'-pyranyloxydeca-2* : 8-*diene-4* : 6-*diyne* (X).—Pent-2-en-4-yn-1-ol (5·5 g.) (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583) was treated, in the manner described above for its 2-methyl derivative, with dihydropyran (6·0 g.) and gave 1-tetrahydro-2'-pyranyloxypent-2-en-4-yne (10·0 g.), b. p. 55—56°/0·3 mm., $n_D^{23}$ 1·4860. Light absorption: see Table 1.

A solution of the tetrahydropyranyl ether (3·0 g.) in alcohol (6 c.c.) was added to one of cuprous ammonium chloride (from 3·0 g. of cuprous chloride and 8·0 g. of ammonium chloride) in water (20 c.c.). The mixture was shaken in oxygen until 100 c.c. had been absorbed. Isolation of the product with ether, and crystallisation from light petroleum (b. p. 40—60°), gave the *bistetrahydropyranyl ether* (2·1 g.) as needles, m. p. 42—43° (Found: C, 72·3; H, 8·05. $C_{18}H_{24}O_4$ requires C, 72·7; H, 7·95%). Light absorption: see Table 1.

Attempts to prepare this bisether from the corresponding glycol (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1589) and dihydropyran were unsuccessful.

*Deca-2* : 8-*diene-4* : 6-*diyne-1* : 10-*diol.*—A solution of the preceding bistetrahydropyranyl ether (500 mg.) and toluene-*p*-sulphonic acid (25 mg.) in alcohol (10 c.c.) was boiled under reflux for 1 hr., and then cooled and concentrated to 5 c.c. under reduced pressure. Water was added and the solid (290 mg.), m. p. 145—148°, thus precipitated was collected. Crystallisation from benzene gave the glycol, m. p. 154—155°, undepressed on admixture with an authentic specimen (*idem, loc. cit.*, give m. p. 155°).

2 : 9-*Dimethyldeca-2* : 8-*diene-4* : 6-*diyne-1* : 10-*diol* (XI).—2-Methylpent-2-en-4-yn-1-ol (7·0 g.) in alcohol (15 c.c.) was added to a solution of cuprous ammonium chloride (from 7 g. of cuprous chloride and 20 g. of ammonium chloride) in 0·05N-hydrochloric acid (60 c.c.). The mixture was shaken in oxygen until 600 c.c. had been absorbed, the precipitated green salts were then dissolved by the addition of dilute hydrochloric acid, and the resulting solution was extracted thoroughly with ether. Evaporation of the extract and crystallisation of the residue (5·5 g.), m. p. 122—124°, from benzene gave the *glycol* as needles, m. p. 129—130° (Found: C, 75·6; H, 7·65. $C_{12}H_{14}O_2$ requires C, 75·65; H, 7·4%). Light absorption: see Table 1.

2 : 9-*Dimethyldeca-2* : 8-*diene-4* : 6-*diynedial* (XIII).—A solution of the preceding glycol (1·0 g.) in acetone (100 c.c.) was shaken with manganese dioxide (20 g.) for 24 hr. Removal of the oxide and solvent gave a solid (0·83 g.), m. p. 108—112°. Crystallisation from methanol yielded the *dialdehyde* as pale yellow plates, m. p. 116—117° (Found: C, 77·7; H, 5·7. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%). Light absorption: see Table 1.

The *dioxime*, purified by precipitation from dioxan solution by addition of water, had m. p. 240° (decomp.; bath preheated to 230°; evacuated capillary) (Found: C, 66·8; H, 5·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%).

2 : 9-*Dimethyldeca-2* : 8-*diene-4* : 6-*diynedioic Acid* (XII).—2-Methylpent-2-en-4-ynoic acid (1·0 g.) in alcohol (10 c.c.) was added to a solution of cuprous ammonium chloride (from 2·0 g. of cuprous chloride and 4·0 g. of ammonium chloride) in 0·02N-hydrochloric acid (15 c.c.). The mixture was shaken in oxygen until 70 c.c. had been absorbed. Dilute hydrochloric acid was then added and the acidic product was isolated in the usual way ($NaHCO_3$), giving a solid (0·82 g.). Purification by precipitation from alcohol with water gave the *acid*, m. p. 292° (decomp.) (Found: C, 66·0, 64·95; H, 5·5, 4·8. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%). Light absorption: Max., 251, 258, 266, 280, 304, 324, and 347 mμ; ε = 25,000, 27,000, 27,000, 25,000, 20,000, 29,500, and 27,500 respectively.

Ethereal diazomethane was added in small portions to a suspension of the acid (400 mg.) in ether (5 c.c.) until a clear solution was obtained. Evaporation, and crystallisation of the residue from methanol, gave the *methyl* ester (400 mg.) as plates, m. p. 88—89° (Found: C, 68·4; H, 6·0. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·75%). Light absorption: see Table 1.

*Methyl* 4 : 11-*Dimethyltetradeca-2* : 4 : 10 : 12-*tetraene-6* : 8-*diynedioate* (XIV).—Malonic acid (1·4 g.) was added to a solution of 2 : 9-dimethyldeca-2 : 8-diene-4 : 6-diyne-1 : 10-dial (0·7 g.) in pyridine (7 c.c.) containing 1 drop of piperidine. The mixture was heated on a steam-bath for 2 hr. The resulting dark red solution was cooled, acidified with mineral acid, and then thoroughly extracted with chloroform. The extract was washed with N-sodium hydroxide, and

the alkaline solution was acidified and extracted with ethyl acetate. Evaporation of the solvent and crystallisation of the residue from acetic acid gave the dioic acid (60 mg.) as prisms, m. p. >325°.

Ethereal diazomethane was added in small portions to a suspension of the acid (45 mg.) in methyl acetate (15 c.c.) until all the acid had reacted and a clear solution was obtained. Evaporation of the solvent and crystallisation of the residue (47 mg.), m. p. 176—179°, from methyl acetate gave the *dimethyl* ester as needles, m. p. 181—182° (Found: C, 72·45; H, 6·25. $C_{18}H_{18}O_4$ requires C, 72·45; H, 6·1%). Light absorption: see Table 1.

5 : 12-*Dimethylhexadeca*-3 : 5 : 11 : 13-*tetraene*-7 : 9-*diyne*-2 : 15-*dione* (XV).—A mixture of 2 : 9-dimethyldeca-2 : 8-diene-4 : 6-diyne-1 : 10-dial (0·5 g.) in acetone (60 c.c.) with aluminium *tert.*-butoxide (1·4 g.) in benzene (80 c.c.) was boiled under reflux for 16 hr., then cooled and poured into dilute sulphuric acid. Isolation of the product with ether and chromatography on alumina (grade IV) from benzene gave a solid (250 mg.), m. p. 142—146°. Crystallisation from benzene–*cyclo*hexane yielded the *diketone* as yellow prisms, m. p. 149—151° (evacuated capillary) (Found: C, 81·6; H, 7·0. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%). Light absorption: see Table 1.

1 : 16-*Bistetrahydro*-2′-*pyranyloxy*-2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 8 : 14-*triene*-4 : 12-*diyne*-6 : 11-*diol*.—Oct-4-ene-2 : 7-dione (2·3 g.) (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089) in ether (150 c.c.) was added to a cooled (0°) ethereal solution (250 c.c.) of the lithium derivative of 2-methyl-1-tetrahydro-2′-pyranyloxypent-2-en-4-yne [prepared in the manner described above from 8·0 g. of the tetrahydropyranyl ether and phenyl-lithium (from 0·62 g. of lithium)]. The temperature of the mixture was allowed to rise to 20° during 8 hr. and the mixture was then boiled for 10 min. and again cooled to 0°. Saturated aqueous ammonium chloride was added, to decompose the lithium complex, and the ethereal layer was separated, washed with water, dried ($Na_2SO_4$), and evaporated under reduced pressure. A suspension of the residue in light petroleum (b. p. 60—80°; 200 c.c.) was shaken with aqueous methanol (15 : 85 v/v; 4 × 100 c.c.). The methanolic solutions were combined, diluted with a large excess of water, and extracted thoroughly with ether. The extract was washed with water, dried ($Na_2SO_4$), and evaporated under reduced pressure, giving the glycol (7·0 g.) as a viscous yellow oil, $n_D^{21}$ 1·5064. Light absorption: Max., 227 and 234 mμ; ε = 35,000 and 30,000 respectively.

1 : 16-*Bistetrahydro*-2′-*pyranyloxy*-2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diyne* (III*b*).—A hot solution of toluene-*p*-sulphonic acid (250 mg.; dried by being melted *in vacuo*) in toluene (100 c.c.) was added to a warm (*ca.* 50°) solution of the preceding glycol (7·0 g.) in toluene (150 c.c.). The mixture was heated rapidly and boiled for *ca.* 3 min., the water which separated being removed by azeotropic distillation. The mixture was cooled in an ice-bath and then washed with a saturated aqueous solution of sodium hydrogen carbonate. The dark red solution was diluted with light petroleum (b. p. 40—60°; 300 c.c.) and extracted with aqueous methanol (15 : 85 v/v; 4 × 100 c.c.). The petroleum solution was washed with water, dried, and evaporated under reduced pressure. The residue, in light petroleum (b. p. 40—60°), was poured on to alumina (grade II—III) and the chromatogram was developed with benzene–light petroleum (b. p. 40—60°) (1 : 1). Evaporation of the product from the main band gave a residue which solidified partly at 0°. Crystallisation from *cyclo*hexane gave the *bistetrahydropyranyl ether* (550 mg.) as yellow needles, m. p. 103° (bath preheated to 90°) (Found: C, 77·65; H, 8·3. $C_{30}H_{40}O_4$ requires C, 77·55; H, 8·6%). Light absorption: see Table 2.

2 : 6 : 11 : 15-*Tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diyne*-1 : 16-*diol* (III*a*).—A solution of the preceding ether (480 mg.) and toluene-*p*-sulphonic acid (30 mg.) in alcohol (10 c.c.) was boiled under reflux for 1 hr., then cooled and concentrated to *ca.* 4 c.c. under reduced pressure. Water was added and the solid (275 mg.), m. p. 96—98°, thus precipitated was collected. Crystallisation from benzene gave the *glycol*, m. p. 101—102° strongly depressed on admixture with the starting material (Found: C, 81·15; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·15%). Light absorption: see Table 2.

2 : 6 : 11 : 15-*Tetramethylhexadeca*-2 : 6 : 8 : 10 : 14-*pentaene*-4 : 12-*diynedial* (XVI).—A solution of the preceding glycol (260 mg.) in acetone (40 c.c.) was shaken with manganese dioxide (6·0 g.) for 24 hr. Removal of the oxide and solvent, and crystallisation of the residue from alcohol, gave the *dialdehyde* (245 mg.) as deep yellow needles, m. p. 137—138° (evacuated capillary) (Found: C, 82·4; H, 7·2. $C_{20}H_{20}O_2$ requires C, 82·15; H, 6·9%). Light absorption in alcohol: see Table 2; in $CHCl_3$, max. 409 mμ (ε = 45,000).

Oxidation of the dialdehyde with silver oxide or, in acetone, with chromic acid, did not yield the corresponding acid.

*Methyl* 4 : 8 : 13 : 17-*Tetramethyleicosa*-2 : 4 : 8 : 10 : 12 : 16 : 18-*heptaene*-6 : 14-*diynedioate* (XVII).—Malonic acid (700 mg.) was added to a solution of the preceding dialdehyde (280 mg.) and piperidine (1 drop) in pyridine (5 c.c.), and the mixture was heated on a steam-bath for 2 hr. The resulting dark red solution was evaporated under reduced pressure, and dilute acetic acid was added to the residue. The orange-red solid was collected and crystallised from acetic acid, giving the dioic acid (105 mg.), m. p. >325°. Light absorption in pyridine: Max., 420 mμ; ε = 43,000.

Esterification of the acid (90 mg.) in pyridine (5 c.c.) with ethereal diazomethane, evaporation of the solvents, and crystallisation of the residue gave the *methyl* ester (60 mg.), m. p. 182—183° (evacuated capillary), which formed orange prisms from chloroform–methanol or needles from ethyl acetate (Found: C, 76·75; H, 7·15. $C_{26}H_{28}O_4$ requires C, 77·1; H, 6·95%). Light absorption: see Table 2.

"*all*-trans"-*Methylbixin* (I).—To determine the optimum conditions for the catalytic reduction of the preceding diester to methylbixin, a series of experiments (on a 5-mg. scale) were carried out, in a micro-hydrogenation apparatus, with ethyl acetate as solvent and a lead-poisoned palladium catalyst (Lindlar, *loc. cit.*). After each hydrogenation the catalyst was removed, and the solution was exposed to diffused daylight for 2 hr. in the presence of a trace of iodine, and then diluted to a standard volume with benzene. The intensity of the light absorption maximum at 475 mμ was taken as a measure of the methylbixin content. As is shown in the following Table the highest yield was obtained after 3 mols. of hydrogen had been absorbed; these conditions were therefore followed in the preparative run described below.

| Mols. of hydrogen | 2·0 | 2·5 | 3·0 | 4·0 | 6·0 |
|---|---|---|---|---|---|
| $E^{1\%}_{1\,cm.}$ (475 mμ) | 180 | 220 | 350 | 250 | 140 |

A solution of the diacetylenic diester (65 mg.) and quinoline (1 drop) in ethyl acetate (30 c.c.) was shaken with Lindlar's catalyst (100 mg.) in hydrogen until 3 mols. had been absorbed (12 c.c. at 26°/750 mm.). The reaction was interrupted, the catalyst and solvent were removed, and the residue, in benzene–light petroleum (b. p. 40—60°) (1 : 1; 20 c.c.), was poured on to a column of alumina (grade IV). The chromatogram was developed with a mixture (1 : 2) of the same solvents, giving (i) a diffuse yellow band (least strongly adsorbed); (ii) a red band; and (iii) a small brown band. The column was divided mechanically and the red band was eluted with acetone. Evaporation of the solvent and crystallisation of the residue from chloroform–methanol gave "all-*trans*"-methylbixin (4—5 mg.), m. p. 200—202° (Kofler block), undepressed on admixture with an authentic specimen, m. p. 200—202° (Kofler block), prepared by isomerisation of methyl natural-bixin [cf. Escue and Zechmeister, *J. Amer. Chem. Soc.*, 1944, **66**, 322, who give m. p. 198° (corr.)]. Light absorption: see Table 2. A mixed chromatogram of the synthetic and the authentic specimen showed no separation.

The yellow band was eluted with acetone, and the solvent was evaporated. The residue and a trace of iodine, in ethyl acetate, were exposed to diffused daylight for 4 hr. The solution was washed with aqueous sodium thiosulphate, dried, and evaporated. Chromatography of the residue in the manner described above gave more crystalline methylbixin (1 mg.). No attempt was made before irradiation to isolate the unstable intermediate.

2 : 2 : 6 : 10 : 15 : 19 : 23 : 23-*Octamethyltetracosa*-4 : 6 : 10 : 12 : 14 : 18 : 20-*heptaene*-8 : 16-*diyne*-3 : 22-*dione* (XVIII*a*).—A mixture of 2 : 6 : 11 : 15-tetramethylhexadeca-2 : 6 : 8 : 10 : 14-pentaene-4 : 12-diynedial (75 mg.) in pinacolone (15 c.c.), with aluminium *tert.*-butoxide (1·5 g.) in benzene (15 c.c.), was boiled under reflux for 15 hr. and then cooled to 0°. Addition of dilute sulphuric acid and isolation of the product in the usual way gave the *diketone* (45 mg.) which crystallised from benzene as yellow needles and from ethyl acetate as orange rods, m. p. 189° (Found: C, 84·45; H, 8·85. $C_{32}H_{40}O_2$ requires C, 84·15; H, 8·8%). Light absorption: see Table 2.

2 : 2 : 6 : 10 : 15 : 19 : 23 : 23-*Octamethyltetracosa*-4 : 6 : 8 : 10 : 12 : 14 : 16 : 18 : 20-*nonaene*-3 : 22-*dione* (XIX*a*).—The preceding diketone (34 mg.) in ethyl acetate (12 c.c.) was shaken with a lead-poisoned palladium catalyst (Lindlar, *loc. cit.*) (50 mg.) in an atmosphere of hydrogen until 3 mols. (5·3 c.c. at 23°/755 mm.) had been absorbed. The catalyst was removed, and iodine (1 mg.) added to the solution which was then kept in diffuse daylight for 6 hr. The solution was washed with aqueous sodium thiosulphate, dried, and evaporated. The residue in benzene (10 c.c.) was poured on a column of alumina (grade IV), and the chromatogram was developed with benzene–light petroleum (b. p. 40—60°) (1 : 1). The column was divided mechanically and the bright red band was eluted with acetone. Evapor-

ation, and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°), gave the diketone as dark red plates (2·5 mg.), m. p. 220—221° (Kofler block). Light absorption : see Table 2.

One of us (R. A.) is indebted to the Royal Commission for the Exhibition of 1851 for an Overseas Scholarship.

Analyses and light-absorption measurements for this and the two following papers were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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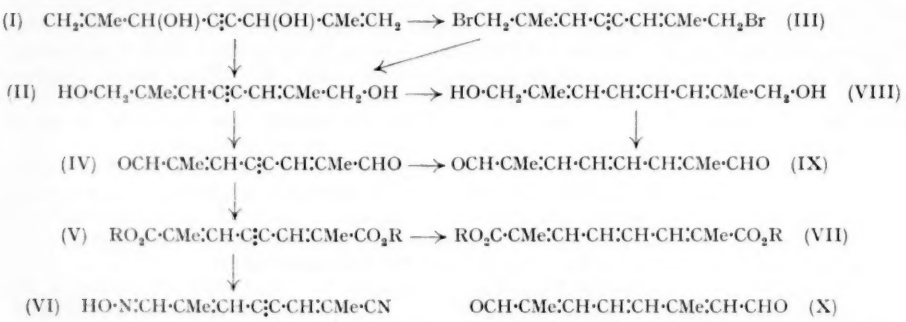
## 652. *Carotenoids and Related Compounds. Part II.** $C_{10}$ *Intermediates for the Synthesis of Carotenoids.*

By Paul Mildner and B. C. L. Weedon.

A number of $C_{10}$ intermediates for the synthesis of carotenoids and derived compounds have been prepared.

All routes so far developed for the total synthesis of a carotenoid consist in the chain extension, in both directions simultaneously, of a small central unit. As the latter, acetylene ($C_2$), diacetylene ($C_4$), and oct-4-ene-2 : 7-dione ($C_8$) have each been employed (for reviews see *Ann. Reports*, 1950—1952). In connection with the programme outlined in Part I (preceding paper), the use of larger intermediates for introducing the central portion of the final molecule seemed to offer certain advantages. The preparation of suitable compounds was therefore undertaken, and in this paper convenient syntheses of a number of $C_{10}$ intermediates are described.


(I) CH2:CMe·CH(OH)·C:C·CH(OH)·CMe:CH2 → BrCH2·CMe:CH·C:C·CH:CMe·CH2Br (III)
(II) HO·CH2·CMe:CH·C:C·CH:CMe·CH2·OH → HO·CH2·CMe:CH·CH:CH·CH:CMe·CH2·OH (VIII)
(IV) OCH·CMe:CH·C:C·CH:CMe·CHO → OCH·CMe:CH·CH:CH·CH:CMe·CHO (IX)
(V) RO2C·CMe:CH·C:C·CH:CMe·CO2R → RO2C·CMe:CH·CH:CH·CH:CMe·CO2R (VII)
(VI) HO·N:CH·CMe:CH·C:C·CH:CMe·CN
OCH·CMe:CH·CH:CH·CMe:CH·CHO (X)

The formation in 50% yield of a crystalline glycol (I) (m. p. 71°), by the Grignard reaction of acetylene with α-methylacraldehyde, was reported by Deemer, Lutwak, and Strong (*J. Amer. Chem. Soc.*, 1948, **70**, 154). Using slightly different experimental conditions we have repeated this reaction several times and always obtained, in similar yield, a higher-melting (92°) form of the glycol; this diastereoisomeride closely resembles a product from one preparation by Deemer *et al.*

The American authors rearranged the low-melting glycol (I) to its fully conjugated isomer (II) by heating it with aqueous alcoholic sulphuric acid. Only low yields (10%) of crystalline product were however isolated, probably owing to partial etherification of the glycol during isomerisation (cf. Heilbron, Jones, and Weedon, *J.*, 1945, 81). In the present studies higher yields (up to 60%) of crystalline diprimary glycol (II) have been obtained by treating (I) with phosphorus tribromide, and hydrolysis of the resulting dibromide (III)

* Part I, preceding paper.

*via* the diacetate. Attempts by Deemer *et al.* to oxidise the glycol (II) to the corresponding dialdehyde, or to reduce it to a triene glycol, were unsuccessful. By methods recently developed, both these transformations have now been effected almost quantitatively.

By oxidation of the diprimary glycol (II), in acetone with manganese dioxide (cf. Part I), the dialdehyde (IV) was prepared (95%). Chromic acid oxidation of the dialdehyde gave in 95% yield the diacid (V; R = H) which was also obtained, but only in 30% yield, by direct oxidation of the glycol (II). Esterification with diazomethane gave the dimethyl ester (V; R = Me). Attempts to prepare the corresponding dinitrile by dehydration of the dioxime of (IV) with acetic anhydride were unsuccessful, the nitrile-oxime (VI) being isolated.

Partial hydrogenation of the diester (V; R = Me) over Raney nickel, or lead-poisoned palladium (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446), gave (90—95%) a triene diester (VII; R = Me) which, by irradiation in the presence of a trace of iodine, was converted into a higher-melting isomer. It is believed that the initial hydrogenation product has a *cis*-configuration about the central double bond, in agreement with the known stereochemical course of reduction over palladium and nickel catalysts (cf. Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 148), and that on irradiation it rearranges into the "all-*trans*"-form. Hydrolysis of the two diesters (VII; R = Me) gave different isomeric dioic acids (VII; R = H), or half esters, depending on the experimental conditions.

Partial reduction of the glycol (II) over Lindlar's catalyst gave, almost quantitatively, a triene glycol (VIII) which was oxidised, in acetone with manganese dioxide, to the triene dialdehyde (IX) in 85% yield. The same product was also obtained (80%) by reduction of the acetylenic dialdehyde (IV).

The triene glycol (VIII) is probably a *trans-cis-trans*-isomer; on irradiation (iodine) it yielded complex mixtures. Surprisingly, the triene dialdehyde (IX) was recovered after irradiation (iodine) or fusion, and it is therefore tentatively assigned the "all-*trans*"-structure, stereomutation about the central bond being assumed to have taken place spontaneously in solution at room temperature. The possibility that the dialdehyde contains a *cis*-double bond which is preserved during irradiation and fusion is considered unlikely, but cannot be definitely excluded. It is noteworthy that a higher-melting $C_{10}$ dialdehyde, exhibiting light-absorption maxima at very similar wave-lengths to those of the synthetic dialdehyde reported above, was isolated (6—8%) by Wendler, Rosenblum, and Tishler (*J. Amer. Chem. Soc.*, 1950, **72**, 234) as a by-product in the oxidation of β-carotene with hydrogen peroxide–osmium tetroxide. From its mode of formation, this degradation product is, presumably, an "all-*trans*"-isomer, and of the two conceivable structures, (IX) and (X), Wendler *et al.* favour (IX). Whether the differences between the two dialdehydes are due to polymorphism, or to structural or geometrical isomerism, is at present uncertain.

| | Acetylenic series | | "Mono-*cis*" series | | "All-*trans*" series | |
|---|---|---|---|---|---|---|
| | $\lambda_{max.}$ | ε | $\lambda_{max.}$ | ε | $\lambda_{max.}$ | ε |
| Glycol (III) or (VIII) ..... | 263 * | 19,500 | — | — | — | — |
| | 271 | 26,000 | 281 | 39,000 | — | — |
| | 287 | 21,000 | 292 | 30,000 | — | — |
| Dialdehyde (IV) or (IX) † ..... | 308 } 327 } | 35,000 | — | — | 306 | 30,000 |
| | | | — | — | 320 | 47,500 |
| | | | | | 336 | 42,500 |
| Diester (V or VII; R = Me) ..... | 305 | 30,000 | 316 | 38,000 | 320 | 51,000 |
| | 322 | 26,000 | 323 * | 32,500 | 330 | 45,000 |
| Half-ester of (V or VII; R = H) | — | — | 315 | 37,000 | 314 | 49,000 |
| | — | — | 323 * | 31,000 | 327 | 39,000 |
| Diacid (V or VII; R = H) ..... | 305 | 26,000 | 315 | 44,000 | 315 | 49,000 |
| | — | — | 327 | 41,000 | 326 | 43,000 |

*Inflexion. † In *n*-hexane.

All the compounds described above exhibited the expected light-absorption properties, most of which are given in the Table (wave-lengths in mμ). The acetylenic compounds have maximal absorption at wave-lengths 10—15 mμ shorter than those of the corresponding polyenes (cf. Part I). As with the geometrical isomers of muconic acid and its derivatives (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235; Elvidge, Linstead, and Sims, *J.*, 1951,

3386; 1953, 1793), the " mono-*cis* "- and " all-*trans* "-form of the acid (VII; R = H), and its di- and half-ester, have maximal absorption at almost identical wave-lengths, but of slightly different intensity.

An account of the work covered by this and the following paper was given at the Chemical Society Symposium on Acetylene Chemistry (cf. *Chem. and Ind.*, 1953, 239). Inhoffen, Isler, Bey, Raspé, Zeller, and Ahrens (*Annalen*, 1953, **580**, 7) meanwhile have reported the preparation of the acetylenic dialdehyde (IV), and its use in the synthesis of crocetin. The glycol (II) was prepared by the method of Deemer *et al.* (the yield from the isomerisation being raised to 30%), and oxidised to (IV) by a process very similar to that described here.

## Experimental

See notes preceding Experimental section of Part I.

**2 : 7-*Dimethylocta*-1 : 7-*dien*-4-*yne*-3 : 6-*diol* (I).**—Benzene (1 l.) was added to a solution of ethylmagnesium bromide (from 24 g. of magnesium) in ether (500 c.c.), and the majority of the ether was then distilled off. The resulting solution was cooled and stirred vigorously. A rapid stream of acetylene (purified by passage through acidified copper sulphate solution, chromic acid, concentrated sulphuric acid, and finally over phosphoric oxide) was passed through the solution for 3 hr. To the pale grey suspension thus obtained freshly distilled α-methylacraldehyde (70 g.) was added during 45 min., and the mixture was stirred overnight, giving a clear solution. The Grignard complex was decomposed by the addition of saturated aqueous ammonium chloride, and the benzene layer was then separated, washed with water, dried ($Na_2SO_4$), and evaporated.

The viscous residue (72 g.) crystallised partly during a few days at 0°. The solid was freed from oil by trituration at 0° with a small amount of benzene. Crystallisation from benzene or chloroform–light petroleum (b. p. 60—80°) gave the glycol as plates (42 g., 50%), m. p. 91—92° (Found : C, 72·25; H, 8·8. Calc. for $C_{10}H_{14}O_2$ : C, 72·25; H, 8·5%) (Deemer, Lutwak, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 154, give m. p. 70·5—71·5°, but in one experiment isolated an isomeric product, m. p. 88—91°).

**1 : 8-*Dibromo*-2 : 7-*dimethylocta*-2 : 6-*dien*-4-*yne* (III).**—Phosphorus tribromide (78 g.) was added dropwise at 20° to a well-stirred suspension of the preceding crystalline glycol (20·0 g.) in benzene (160 c.c.), and the mixture was stirred for a further 5 hr. Ice and water were added and the mixture was extracted with ether (3 × 70 c.c.). The combined extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated. The residue crystallised at 0°. Low-temperature crystallisation from light petroleum (b. p. 60—80°) gave the *dibromide* as needles (25 g., 70%), m. p. 49—50° (Found : C, 41·05; H, 4·3. $C_{10}H_{12}Br_2$ requires C, 41·1; H, 4·15%). Light absorption : Max., 293 mμ; ε = 27,500. Inflexions, 279 and 302 mμ; ε = 23,000 and 23,000. Distillation of the crude dibromide gave a product, b. p. 108—110°/$10^{-3}$ mm., m. p. 47—49°, in only 50% yield.

**2 : 7-*Dimethylocta*-2 : 6-*dien*-4-*yne*-1 : 8-*diol* (II).**—A solution of the preceding dibromide (25·0 g.) and anhydrous potassium acetate (24 g.) in methanol (300 c.c.) was stirred and boiled under reflux for 3—12 hr. Most of the solvent was evaporated at 20° under reduced pressure, water was added, and the product was isolated with ether, giving an oil (19·2 g., 90%) which, in methanol (55 c.c.), was warmed at 50—55° with methanolic N-potassium hydroxide (380 c.c.) for 20 min. The solution was rapidly cooled and then concentrated under reduced pressure. Water was added and the product was isolated with ether. Crystallisation from acetone–light petroleum (b. p. 60—80°) gave the glycol (12·0 g.) as needles, m. p. 113° (Found : C, 71·95; H, 8·35. Calc. for $C_{10}H_{14}O_2$ : C, 72·25; H, 8·5%). Light absorption : see Table. [*Idem*, *loc. cit.*, give m. p. 109—110° and light absorption : max., 270, 286, and 333 mμ (ε = 27,000, 21,000, and 1400 respectively).]

The yield in the hydrolysis was variable (50—90%). In some experiments the crude diacetate was distilled, giving an oil, b. p. 120°(bath-temp.)/$10^{-4}$ mm., $n_D^{25}$ 1·5170.

Bromination of the crude viscous product obtained from the Grignard reaction after removal of the crystalline glycol (I), and subsequent hydrolysis of the resulting dibromide, gave the rearranged glycol, m. p. 113°, in *ca.* 10% overall yield.

**2 : 7-*Dimethylocta*-2 : 6-*dien*-4-*ynedial* (IV).**—The preceding glycol (3·0 g.) in acetone (300 c.c.) was shaken with manganese dioxide (60 g.) at 20° for 24 hr. Removal of oxide and solvent, and crystallisation of the residue (2·9 g.), m. p. 67—68°, from aqueous methanol gave the dialdehyde as needles, m. p. 69·5—70° (Found : C, 74·15; H, 6·4. Calc. for $C_{10}H_{10}O_2$ : C,

75·05; H, 6·2%) (Inhoffen, Isler, Bey, Raspé, Zeller, and Ahrens, *Annalen*, 1953, **580**, 7, give m. p. 68°). Light absorption: see Table. The *dioxime*, prepared in 85% yield, crystallised from aqueous pyridine in needles, m. p. 234·5° (Found: N, 14·6. $C_{10}H_{12}O_2N_2$ requires N, 14·55%). Light absorption: Max., 324 and 343 mμ; ε = 42,500 and 38,500 respectively.

*7-Cyano-2-methylocta-2 : 6-dien-4-ynaldoxime* (VI).—A solution of the preceding dialdoxime (220 mg.) in acetic anhydride (66 c.c.) was heated under reflux for 15 min. and then evaporated. Chromatography of the residue in benzene on alumina (*ca.* 50 g.; grade IV), and elution of the main pale yellow band with benzene–methanol (95 : 5), yielded a solid (170 mg.), m. p. 148°. Crystallisation from aqueous methanol gave the *nitrile-oxime* as needles, m. p. 152° (Found: C, 68·75; H, 6·0. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8%). Light absorption: Max., 319 and 328 mμ; ε = 31,500 and 31,500.

*2 : 7-Dimethylocta-2 : 6-dien-4-ynedioic Acid* (V; R = H).—(a) *From 2 : 7-dimethylocta-2 : 6-dien-4-ynedial.* A solution of chromium trioxide (1·4 g.) and concentrated sulphuric acid (2·24 g.) in water (7 c.c.) was added to a stirred and cooled (ice-bath) solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (1·37 g.) in acetone (40 c.c.) at such a rate as to keep the temperature at 10°. The mixture was stirred for 2 hr. at 20°, diluted with water, and then thoroughly extracted with ether. The acidic material was isolated by extraction of the ethereal solution with saturated aqueous sodium hydrogen carbonate in the usual way, giving a pale yellow powder (1·55 g., 95%), m. p. 287°. Recrystallisation from aqueous methanol gave the *diacid* as a colourless microcrystalline powder, m. p. 302° (Found: C, 61·6; H, 5·7. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%). Light absorption: see Table.

All attempts to obtain the acid by oxidation of the dialdehyde with freshly prepared silver oxide (cf. Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719) failed.

(b) *From 2 : 7-dimethylocta-2 : 6-dien-4-yne-1 : 8-diol.* A solution (16 c.c.) of chromium trioxide (3·2 g.) and concentrated sulphuric acid (5·12 g.) in water was added to a stirred and cooled solution of 2 : 7-dimethylocta-2 : 6-dien-4-yne-1 : 8-diol (1·0 g.) in acetone (20 c.c.) during 30 min., the temperature being kept below 15°. The mixture was stirred at 20° for 2 hr., diluted with water, and then thoroughly extracted with ether. The acidic product was isolated ($NaHCO_3$) and gave the crude diacid (0·35 g., 30%) as a pale yellowish powder, m. p. 278°. Recrystallisation from aqueous methanol, or from acetone–light petroleum (b. p. 60—80°) gave the diacid as a colourless microcrystalline powder, m. p. and mixed m. p. with a specimen from (a), 302°.

*Methyl 2 : 7-Dimethylocta-2 : 6-dien-4-ynedioate* (V; R = Me).—To a suspension of the preceding acid (1·55 g.) in dry ether (15 c.c.) ethereal diazomethane was added at 20° in small portions, until no more nitrogen was evolved and a homogeneous solution obtained. The solution was filtered and evaporated. The residue crystallised from chloroform–light petroleum (b. p. 60—80°), or from methanol, giving the *diester* as needles (1·38 g., 78%), m. p. 113—114° (Found: C, 64·9; H, 6·45. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). Light absorption: see Table.

Hydrolysis of the ester (100 mg.) with potassium hydroxide (1·60 g.) in methanol (50 c.c.) for 48 hr. at 20°, and isolation of the product in the usual manner, furnished the original acid (85 mg., 98%), m. p. and mixed m. p. 302°.

*Methyl 2 : 7-Dimethylocta-trans-2 : cis-4 : trans-6-trienedioate* (V; R = Me).—(*a*) The preceding diester (130 mg.) in ethyl acetate (10 c.c.) was shaken with Lindlar's catalyst (25 mg.; no quinoline) in hydrogen until 15·25 c.c. at 23°/758 mm. (equiv. to 1·07 double bonds) had been absorbed (rate of absorption *ca.* 4 c.c./min.). The reaction was then interrupted, the catalyst and solvent were removed, and the residue was crystallised from methanol, giving the " *mono*-cis "-*diester* (126 mg.) as needles, m. p. 98° (Found: C, 64·7; H, 6·9. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%). Light absorption: see Table.

When the hydrogenation was carried out in the presence of quinoline (4%), the rate of absorption was much slower (0·4—0·8 c.c./min.), and a sharp drop in rate was observed when 1 mol. of hydrogen had been taken up. The yield of product was the same (95%).

(*b*) The acetylenic diester (100 mg.) in methanol (30 c.c.) was shaken with Raney nickel (0·3 g.) in hydrogen until 1·2 mols. had been absorbed (3 c.c./min.). The reaction was then interrupted and the product isolated, giving the " mono-*cis* "-diester (90 mg.), m. p. 98°, undepressed on admixture with a sample from (*a*).

Repetition of this experiment in the presence of piperidine (2 c.c.) and zinc acetate dihydrate (0·1 g.) (cf. Oroshnik, Karmas, and Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 295) gave the same yield (90%) of product (the rate of absorption was 1 c.c./min., but fell to 0·4 c.c./min. near the end of the reaction).

*Methyl "all*-trans"-2 : 7-*Dimethylocta*-2 : 4 : 6-*trienedioate* (V; R = Me).—A solution of the preceding mono-*cis*-triene diester [177 mg.; from (*a*)], and a trace of iodine, in light petroleum (b. p. 60—80°) (20 c.c.) was irradiated with ultra-violet light for 4 hr. at 20°. The petroleum solution was washed with N-sodium thiosulphate and water, dried, and evaporated. The residue was crystallised from methanol giving the "*all*-trans"-*diester* as needles (150 mg.), m. p. 140—141° (Found: C, 64·55; H, 7·45%). Light absorption: see Table.

*Methyl Hydrogen* 2 : 7-*Dimethylocta*-trans-2 : cis-4 : trans-6-*trienedioate*.—Hydrolysis of the "mono-*cis*"-triene diester (38 mg.) with potassium hydroxide (0·64 g.) in methanol (20 c.c.) for 48 hr. at 20° gave the *half-ester* which crystallised from aqueous methanol as needles (30 mg.), m. p. 256° (Found: C, 62·35; H, 6·9. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%). Light absorption: see Table.

*Methyl Hydrogen "all*-trans"-2 : 7-*Dimethylocta*-2 : 4 : 6-*trienedioate*.—Hydrolysis of the "all-*trans*"-triene diester (17 mg.) with potassium hydroxide (0·64 g.) in methanol (20 c.c.) for 48 hr. at 20° gave the *half-ester* which separated from aqueous methanol as a microcrystalline powder (12 mg.), m. p. 292° (Found: C, 62·75; H, 7·15%). Light absorption: see Table.

2 : 7-*Dimethylocta*-trans-2 : cis-4 : trans-6-*trienedioic Acid* (VII; R = H).—Hydrolysis of the "mono-*cis*"-triene diester (53 mg.) with methanolic N-potassium hydroxide (35 c.c.) for 96 hr. at 20° gave the *diacid* which separated from aqueous methanol as crystals (37 mg.), m. p. 266° (Found: C, 61·4; H, 6·15. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·15%). Light absorption: see Table.

"*all*-trans-"-2 : 7-*Dimethylocta*-2 : 4 : 6-*trienedioic Acid* (VII; R = H).—Hydrolysis of the "all-*trans*"-diester (69 mg.) with methanolic N-potassium hydroxide (50 c.c.) for 6 days at 20° gave the *diacid* which separated from aqueous methanol as crystals (50 mg.), m. p. 315° (Found: C, 61·3; H, 6·5%). Light absorption: see Table.

2 : 7-*Dimethylocta*-2 : 4 : 6-*triene*-1 : 8-*diol* (VIII).—A solution of 2 : 7-dimethylocta-2 : 6-dien-4-yne-1 : 8-diol (1·0 g.) in ethyl acetate (50 c.c.) containing quinoline (1 drop) was shaken in hydrogen with Lindlar's catalyst (0·1 g.). When 1 mol. of hydrogen had been taken up (150 c.c. at 21°/767 mm.) the rate of absorption fell markedly, and the reaction was interrupted. Isolation of the product and crystallisation from acetone gave the *glycol*, in almost quantitative yield, as needles, m. p. 137° (Found: C, 71·65; H, 9·85. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Light absorption: see Table.

Irradiation of the glycol in ethyl acetate, containing a trace of iodine, with ultra-violet light for 4 hr. gave a mixture.

2 : 7-*Dimethylocta*-2 : 4 : 6-*triene*-1 : 8-*dial* (IX) (with RASHID AHMAD).—(*a*) The preceding glycol (2·0 g.) in acetone (200 c.c.) was shaken with manganese dioxide (40 g.) at 20° for 24 hr. Removal of oxide and solvent, and crystallisation of the residue from benzene or aqueous methanol, gave the *dialdehyde* as yellow prisms (1·8 g.), m. p. 151—151·5° (Found: C, 73·2; H, 7·55. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%). Light absorption: see Table.

(*b*) A solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (1·0 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen with Lindlar's catalyst (0·7 g.). After 1 mol. of hydrogen (150 c.c. at 20°/755 mm.) had been absorbed, the reaction was interrupted. Removal of catalyst and solvent, and crystallisation of the residue (0·95 g.), m. p. 137—140°, twice from benzene gave the triene dialdehyde (0·8 g.), m. p. 151°, undepressed on admixture with a specimen from (*a*).

The dialdehyde was recovered after irradiation with ultra-violet light (in the presence of a trace of iodine) for 4 hr. in ethyl acetate or chloroform, or for 24 hr. in ether; also after fusion for 3 min. followed by crystallisation of the product from benzene.

By oxidation of β-carotene with hydrogen peroxide–osmium tetroxide, Wendler, Rosenblum, and Tishler (*J. Amer. Chem. Soc.*, 1950, **72**, 234) obtained a $C_{10}$ triene dialdehyde which crystallised from benzene–light petroleum in light orange needles, m. p. 168°. Light absorption in *iso*octane: Max., 306, 320, and 336 mμ; ε = 38,000, 59,500, and 54,000. [The authors are indebted to Dr. N. L. Wendler (personal communication) for the ε values; figures given in the Experimental section of their paper quoted are incorrect.]

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## 653. *Carotenoids and Related Compounds. Part III.* The Synthesis of a Bisnorcrocetin, a Pentaene Degradation Product of Azafrin, and Other Polyenes.*

By Rashid Ahmad and B. C. L. Weedon.

Condensations of the Doebner and the Claisen type with 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (I) and 2 : 7-dimethylocta-2 : 4 : 6-trienedial (II) have been studied, and used to synthesise a bisnorcrocetin, the azafrin degradation product methyl 4 : 9-dimethyldodecapentaenedioate (IV), an isomer of azafrinal-II methyl ester (III), and other polyenes.

In the preceding paper the two $C_{10}$ dialdehydes (I) and (II) were described. Progress made in developing synthetical routes, based on these intermediates, to carotenoids and related compounds is now reported.

Condensations of the Doebner type have been used extensively to prepare polyene acids from αβ-unsaturated aldehydes (cf. Jones, *Ann. Reports*, 1941, **38**, 178). Such reactions with dialdehydes have received little study (Part I) but, applied to (I) and (II), offered routes to two of Kuhn and Brockmann's (*Annalen*, 1935, **516**, 95) azafrin degradation products, *viz.*, " azafrinal-II methyl ester " (III) and methyl 4 : 9-dimethyldodecapentaenedioate (IV). Condensation of the acetylenic dialdehyde (I) with malonic acid, and esterification of the initial product, gave (10% overall yield) the aldehydo-ester (V) which was characterised as its oxime. Partial reduction of (V) over Lindlar's catalyst (*Helv. Chim. Acta*, 1952, **35**, 446) led to the corresponding polyene (III). This exhibits light-absorption maxima at wave-lengths very similar to those of " azafrinal-II methyl ester," but its melting point, and that of its oxime, differ appreciably from the values reported by Kuhn and Brockmann (see Experimental section). The two specimens are, presumably, either polymorphs or geometrical isomers.

(I) OCH·CMe:CH·C:::C·CH:CMe·CHO OCH·CMe:CH·CH:CH·CH:CMe·CHO (II)

(V) OCH·CMe:CH·C:::C·CH:CMe·CH:CH·$CO_2$Me

(III) OCH·CMe:CH·CH:CH·CH:CMe·CH:CH·$CO_2$Me

(IV) $MeO_2C$·CH:CH·CMe:CH·CH:CH·CH:CMe·CH:CH·$CO_2$Me

(VI) $MeO_2C$·CR:CH·CH:CH·CMe:CH·CH:CH·CH:CMe·CH:CH·CH:CR·$CO_2$Me

(VII) $RO_2C$·CH:CMe·C(:CH·CMe:CH·CH:CH·CH:CMe·CH:C·CMe:CH·$CO_2$R)($CO_2$R)($CO_2$R)

(VIII) OC·CH:CMe·C(:CH·CMe:CH·CH:CH·CH:CMe·CH:C·CMe:CH·CO)(O——CO)(CO——O)

(IX) $Me_3C$·CO·CH:CH·CMe:CH·C:::C·CH:CMe·CH:CH·CO·$CMe_3$

(X) $Me_3C$·CO·CH:CH·CMe:CH·CH:CH·CH:CMe·CH:CH·CO·$CMe_3$

With the triene dialdehyde (II), in the presence of piperidine, condensation with malonic acid occurred at both ends of the molecule. After esterification of the initial product, the pentaene diester (IV) was obtained (10%). Its melting point and wave-length of maximal absorption are in excellent agreement with those reported for the degradation product of azafrin (*idem, loc. cit.*).

Ethyl ethylidenemalonate, CHMe:$C(CO_2Et)_2$ has previously been used in reactions of the Doebner type with aromatic aldehydes (Gardner, Horton, Thompson, and Twelves, *J. Amer. Chem. Soc.*, 1952, **74**, 5527). Condensation of this ester with the triene dialdehyde (II), followed by partial hydrolysis of the initial product and re-esterification with diazomethane, gave the heptaene tetra-ester (VI; R = $CO_2$Et). Total hydrolysis of the initial product, and decarboxylation of the resulting tetra-acid, yielded a " bisnorcrocetin " which was isolated as its methyl ester (VI; R = H). As expected, the latter exhibits light-absorption maxima at wave-lengths exactly half-way between those of the esters of natural

* Part II, preceding paper.

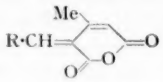
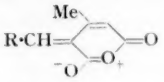
crocetin (VI; R = Me) and of Kuhn and Grundmann's (*Ber.*, 1937, **70**, 1318) synthetic "descrocetin," *i.e.*, crocetin without the four side-chain methyl groups (see Table). Preliminary attempts to condense the triene dialdehyde (II) with methyl tiglate, $CHMe{:}CMe{\cdot}CO_2Me$, have given very erratic results, but, in one run in pyridine–ether with potassium ethoxide as condensing agent, a crude product was obtained which showed the two characteristic light-absorption maxima of crocetin.

An alternative route to heptaenes of the crocetin type is illustrated by the preparation of the tetra-acid (VII; R = H), in 17% yield, by condensation of the triene dialdehyde (II) with methyl β-methylglutaconate (cf. Petrow and Stephenson, *J.*, 1950, 1310; Baxter, *Fortschritte der Chemie organischer Naturstoffe*, 1952, **9**, 65). The tetra-acid and its ester (VII; R = Me) exhibit maximal light absorption of lower intensity, and at much shorter wave-lengths, than either crocetin ester (VI; R = H) or the tetra-ester (VI; R = $CO_2Et$) (see Table). Similar hypsochromic and hypochromic shifts have been noted in the spectra

| | $\lambda_{max.}$ (mμ) | ε | Solvent |
|---|---|---|---|
| Acetylenic aldehydo-ester (V) | 338 | 46,000 | EtOH |
| | 352 | 41,000 | |
| Polyene aldehydo-ester (III) | 330 | 38,000 | *n*-Hexane |
| | 348 | 57,000 | |
| | 367 | 55,000 | |
| Azafrinal-II methyl ester [1] | 331 | — | *n*-Hexane |
| | 351 | — | |
| | 365 | — | |
| Pentaene diester (IV,) synthetic | 389 | 45,000 | $CS_2$ |
| | 412 | 43,000 | |
| ,, (IV), from azafrin [1] | 413 | — | $CS_2$ |
| Methyl ester of crocetin (VI; R = Me) [2] | 434 | — | $CHCl_3$ |
| | 463 | — | |
| Methyl ester of bisnorcrocetin (VI; R = H) | 427 | 110,000 | $CHCl_3$ |
| | 453 | 102,000 | |
| Methyl ester of "descrocetin" [3] | 418 | — | $CHCl_3$ |
| | 444 | — | |
| Tetra-ester (VI; R = $CO_2Et$) | 452 | 75,000 | $CHCl_3$ |
| | 473 | 70,500 | |
| Tetra-acid (VII; R = H) | 385 | 40,000 | EtOH |
| | 390 | 62,000 | 2% KOH |
| ,, ,, | 400 * | 50,000 | 2% KOH |
| Tetra-ester (VII; R = Me) | 395 | 45,000 | $CHCl_3$ |
| | 412 | 41,500 | |
| Dianhydride (VIII) | 476 | 47,500 | $CHCl_3$ |
| Vitamin A acid [4] | 353 | 45,500 | EtOH |
| 4-Carboxyvitamin A acid [5] | 320 | 30,500 | $Pr^iOH$ |
| 4-Carboxyvitamin A acid anhydride [5] | 435 | 34,000 | *cyclo*Hexane |
| Acetylenic diketone (IX) | 376 | 40,500 | $CHCl_3$ |
| | 393 | 37,500 | |
| Pentaene diketone (X) | 398 | 58,000 | $CHCl_3$ |
| | 420 | 53,000 | |

* Inflexion. [1] Kuhn and Brockmann, *Annalen*, 1935, **516**, 95. [2] Kuhn and Winterstein, *Ber.*, 1933, **66**, 209. [3] Kuhn and Grundmann, *Ber.*, 1938, **71**, 2274. [4] Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719. [5] Petrow and Stephenson, *J.*, 1950, 1310.

of other alkylideneglutaconic acids, and ascribed to steric interference of resonance as the result of the $C_{(4)}$-carboxyl substituent (Petrow and Stephenson, *loc. cit.*). Treatment of the tetra-acid (VII; R = H) with acetic anhydride furnished the dianhydride (VIII) which, as expected, shows maximal absorption at much longer wave-lengths than (VII; R = H). To account for the pronounced spectral differences between alkylideneglutaconic acids and their anhydrides, Petrow and Stephenson (*loc. cit.*) have suggested that resonance in the latter involves canonical forms such as (*a*) and (*b*).

(*a*)  (*b*) 

Both the dialdehydes (I) and (II) condense normally with methyl ketones. Thus with pinacolone the diketones (VIII) and (IX) were obtained in 30 and 35% yield respectively.

## Experimental

See notes preceding Experimental section of Part I.

*Methyl 9-Formyl-4 : 9-dimethylnona-2 : 4 : 8-trien-6-ynoate* (V) (with Paul Mildner).—Malonic acid (1·0 g.) was added to a solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (1·0 g.) in pyridine (10 c.c.), and the mixture was heated on a steam-bath for 1 hr. and then cooled. Excess of 2N-sulphuric acid was added and the product was extracted with ether. Evaporation of the extract gave a crude acid (400 mg.) which was treated with ethereal diazomethane. Evaporation of the solution and crystallisation of the residue from methanol gave the *aldehydo-ester* (150 mg.) as pale yellow plates, m. p. 88—89° (Found : C, 71·45; H, 6·8. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·45%). Light absorption : see Table. The *oxime* crystallised from methanol as yellow prisms, m. p. 156° (Found : N, 6·2. $C_{13}H_{15}O_3N$ requires N, 6·0%).

*Methyl 9-Formyl-4 : 9-dimethylnona-2 : 4 : 6 : 8-tetraenoate* (III).—The preceding aldehydo-ester (45 mg.) in methyl acetate (5 c.c.) was shaken with Lindlar's catalyst (50 mg.) (without quinoline) in hydrogen until absorption ceased (5 c.c. at 22°/750 mm., equiv. to 1·0 double bond). The catalyst was filtered off, and the filtrate was irradiated with ultra-violet light for 2 hr. after the addition of a trace of iodine. Evaporation of the solvent, and crystallisation of the residue from methanol, gave the ester (21 mg.) as prisms, m. p. 129°. Light absorption : see Table. [Kuhn and Brockmann (*Annalen*, 1935, **516**, 95) give m. p. 106° for azafrinal-II methyl ester.] The *oxime* crystallised from methanol as yellow prisms, m. p. 177—178° (Found : N, 16·25. $C_{13}H_{17}O_3N$ requires N, 15·95%) (*idem, loc. cit.*, give m. p. 194° for the oxime of azafrinal-II methyl ester).

*Methyl 4 : 9-Dimethyldodeca-2 : 4 : 6 : 8 : 10-pentaenedioate* (IV).—Malonic acid (500 mg.) was added to a solution of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (200 mg.) and piperidine (1 drop) in pyridine (4 c.c.). The mixture was heated on a steam-bath for 2 hr. and then cooled. Excess of 2N-sulphuric acid was added, and the product was extracted with ethyl acetate. The extract was washed thoroughly with saturated aqueous hydrogen carbonate, and the combined washings were then acidified. The crude acid thereby precipitated was collected, washed with ether, and treated with excess of ethereal diazomethane. Evaporation of the resulting solution, and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°), gave the diester (30 mg.) as yellow plates, m. p. 177° (Found : C, 69·7; H, 7·3. Calc. for $C_{16}H_{20}O_4$ : C, 69·5; H, 7·65%). Light absorption : see Table (*idem, loc. cit.*, give m. p. 176°).

*Methyl 2 : 15-Bisethoxycarbonyl-6 : 11-dimethylhexadeca-2 : 4 : 6 : 8 : 10 : 12 : 14-heptaene-dioate* (VI; R = $CO_2Et$).—Aqueous benzyltrimethylammonium hydroxide (1·0 c.c.; 40%) was added to 2 : 7-dimethylocta-2 : 4 : 6-trienedial (100 mg.) and ethyl ethylidenemalonate (1·0 c.c.) in alcohol (10 c.c.), and the solution was kept at 20° for 24 hr. More quaternary ammonium hydroxide solution (1·5 c.c.) was added, and the mixture was boiled under reflux for 15 min. and then cooled and poured into excess of 2N-hydrochloric acid. Extraction of the product with ethyl acetate, and isolation of the acidic fraction in the usual way ($NaHCO_3$), gave a product which was treated with ethereal diazomethane. Evaporation of the solvents, chromatography of the residue, in benzene–light petroleum (b. p. 40—60°) (1 : 2), on alumina (grade IV), and isolation of the single red band gave the *tetra-ester* which crystallised from methyl acetate as bright red plates (9 mg.), m. p. 158—160° (Kofler block) (Found : C, 65·9; H, 7·1. $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·8%). Light absorption : see Table.

*Methyl 6 : 11-Dimethylhexadeca-2 : 4 : 6 : 8 : 10 : 12 : 14-heptaenedioate* (VI; R = H).—Aqueous benzyltrimethylammonium hydroxide (3 c.c.; 40%) was added to 2 : 7-dimethylocta-2 : 4 : 6-trienedial (250 mg.) and ethyl ethylidenemalonate (3 c.c.) in alcohol (25 c.c.), and the solution was kept at 20° for 24 hr. More quaternary base solution (10 c.c.) was added, and the mixture was boiled under reflux for 20 min. and then cooled and poured into excess of 2N-hydrochloric acid. Extraction of the product with ethyl acetate, and isolation of the acidic fraction ($NaHCO_3$), gave a solid tetra-acid which was dissolved in acetic acid (10 c.c.) and acetic anhydride (10 c.c.). The solution was boiled under reflux for 2 hr., cooled, and evaporated under reduced pressure. The residue was washed with ether, suspended in chloroform, and treated with excess of ethereal diazomethane. Evaporation of the resulting solution, chromatography of the residue on alumina (grade IV) from benzene–light petroleum (b. p. 40—60°) (1 : 2), and isolation of the single red band gave the diester which crystallised from chloroform–methanol as red plates (1 mg.), m. p. 218—220° (Kofler block). Light absorption : see Table.

*4 : 13-Dicarboxy-3 : 14-dimethylhexadeca-2 : 4 : 6 : 8 : 10 : 12 : 14-heptaenedioic Acid* (VII; R = H).—A solution of potassium hydroxide (2·3 g.) in methanol (10 c.c.) was added to one of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (500 mg.) and methyl β-methylglutaconate (1·1 g.) in

methanol (15 c.c.). The mixture was kept at 55—60° for 1½ hr. and then for 12 hr. at 0°. The potassium salts which had separated were collected, washed with ethyl acetate, and treated with excess of 2N-sulphuric acid. The mixture was extracted with ethyl acetate, and the extract was washed with warm dilute mineral acid (to remove β-methylglutaconic acid), dried ($Na_2SO_4$), and evaporated, giving a solid (250 mg.), m. p. 205—210°. Light absorption : Max., 385 mμ; $E^{1\%}_{1\,cm.}$ = 900. Crystallisation from aqueous methanol gave the tetra-acid, m. p. 238°. Light absorption : Max., 385 mμ; $E^{1\%}_{1\,cm.}$ = 950 (see Table). Treatment of the tetra-acid with ethereal diazomethane, and purification of the product by chromatography on alumina (grade IV) from benzene–light petroleum (b. p. 40—60°), and crystallisation from the same solvent, gave the *tetra-ester* (VII; R = Me) as prisms, m. p. 157—160° (Found : C, 65·45; H, 7·1. $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·85%). Light absorption : see Table.

A suspension of the tetra-acid (50 mg.) in acetic anhydride (2 c.c.) and ethyl acetate (10 c.c.) was kept at 60—65° until a homogeneous red solution was obtained (1½ hr.). Alcohol (2 c.c.) was added, the mixture was concentrated (to 3 c.c.) under reduced pressure, and the residual solution was kept at 0°. The solid which separated was collected and crystallised from ethyl acetate, giving the *dianhydride* as violet needles (10 mg.), m. p. 193° (Kofler block) (Found : C, 69·45; H, 5·55. $C_{22}H_{20}O_6$ requires C, 69·4; H, 5·3%). Light absorption : see Table.

2 : 2 : 6 : 11 : 15 : 15-*Hexamethylhexadeca*-4 : 6 : 10 : 12-*tetraene*-8-*yne*-3 : 14-*dione* (IX).—A solution of 2 : 7-dimethylocta-2 : 6-dien-4-ynedial (100 mg.) in pinacolone (10 c.c.), and one of aluminium *tert.*-butoxide (2·0 g.) in benzene (20 c.c.), were heated together under reflux for 16 hr., then cooled and poured into 2N-sulphuric acid. Isolation of the product with ether, and crystallisation from benzene, gave the *diketone* (45 mg.) as yellow needles, m. p. 196°, containing benzene of crystallisation (Found : C, 82·95; H, 9·25. $C_{22}H_{30}O_2,C_6H_6$ requires C, 83·2; H, 8·95%). Recrystallisation from chloroform–light petroleum (b. p. 40—60°) gave a solvent-free product, m. p. 196° (Found : C, 80·65; H, 9·55. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·25%). Light absorption : see Table.

2 : 2 : 6 : 11 : 15 : 15-*Hexamethylhexadeca*-4 : 6 : 8 : 10 : 12-*pentaene*-3 : 14-*dione* (X).—A solution of 2 : 7-dimethylocta-2 : 4 : 6-trienedial (75 g.) in pinacolone (10 c.c.), and one of aluminium *tert.*-butoxide (1·5 g.) in benzene (15 c.c.), were heated together under reflux for 12 hr. Isolation of the product as in the preceding experiment, and crystallisation from benzene, gave the *diketone* (50 mg.) as yellow plates, m. p. 209° (Found : C, 80·7; H, 9·75. $C_{22}H_{32}O_2$ requires C, 80·45; H, 9·75%). Light absorption : see Table.

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## 654. *Studies in Mycological Chemistry. Part I. Flaviolin,* 2(*or* 3) : 5 : 7-*Trihydroxy*-1 : 4-*naphthaquinone, a Metabolic Product of* Aspergillus citricus (*Wehmer*) *Mosseray.*

By B. D. Astill and John C. Roberts.

The isolation of flaviolin, a metabolic product of *Aspergillus citricus*, is described. From a consideration of its properties and of the general properties of its triacetyl and *O*-trimethyl derivatives, together with the demonstration that its triacetyl derivative can be degraded to 3 : 5-dihydroxyphthalic acid, it is concluded that flaviolin is 2(or 3) : 5 : 7-trihydroxy-1 : 4-naphthaquinone.

*Aspergillus citricus* (Wehmer) Mosseray is a mould belonging to the *A. niger* group (Thom and Raper, "A Manual of the Aspergilli," Williams and Wilkins Coy., Baltimore, 1945). The particular strain of *A. citricus* used in the present work was originally used in these laboratories because of its ability to produce citric acid from glucose (B. Shaw, Thesis, London, 1950). When this mould was grown on an aqueous medium containing glucose and inorganic salts the substrate became gradually yellow (between approximately the fifth and the eleventh day of incubation at 29°) but, later, the colour changed rapidly

(within one day) to a dark port-wine red. This rapid colour change was found to be coincident with the virtual disappearance of glucose from, and the alkalinisation of, the substrate (see Fig. 1). This paper records our investigations on the pigment responsible for the production of this red colour.

Ether-extraction of the acidified, concentrated substrate yielded a dark red paste. Purification of this material by partition chromatography on columns of powdered cellulose, impregnated with a phosphate buffer, produced an amorphous, red substance which separated slowly from solutions in dioxan, or benzene–dioxan, as small, garnet-red rhombs which, under the normal conditions for determination of m. p., decomposed at about 250°. (Prolonged maintenance at considerably lower temperatures also led to decomposition.) A total of about 2 g. of crystalline pigment was obtained for this work from approximately 800 l. of substrate.

We propose the name, flaviolin, for this pigment because of its remarkable colour properties in aqueous solution (see below). Crystalline flaviolin apparently contained

FIG. 1.

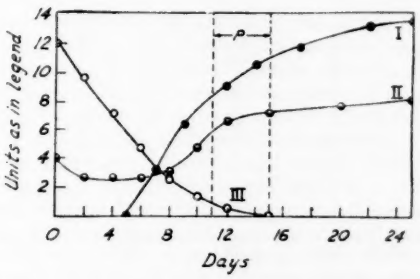



FIG. 2.

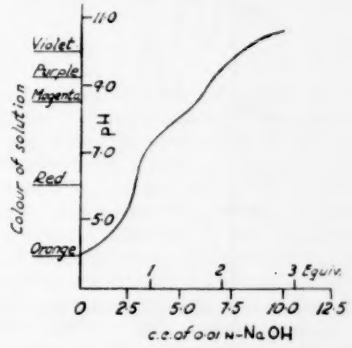



FIG. 1. *Course of flaviolin production. I, Concn. of flaviolin (mg./l.). II,* pH. *III, Concn. of glucose monohydrate (g./200 c.c.). P, Period during which substrates of individual flasks changed from yellow to red.*

FIG. 2. *Titration curve for flaviolin* ($C_{10}H_6O_5,\frac{1}{3}H_2O$, *equiv. to* 3NaOH).

dioxan of crystallisation as well as a small quantity of water of crystallisation. Loss of dioxan, which occurred quite readily, led to an amorphous product. The water of crystallisation was more tenaciously held. These properties invalidated any attempts to determine the molecular weight by crystallographic or other methods. Analysis detected no elements other than carbon and hydrogen and gave zero results for *C*-methyl (Kuhn–Roth) and methoxyl groups (Zeisel). With the aid of information, concerning the structure of flaviolin, which was later acquired from a study of its derivatives, we ascribe to amorphous flaviolin the molecular formula $C_{10}H_6O_5,\frac{1}{3}H_2O$.

An aqueous solution of flaviolin showed a spectacular series of colour changes as the pH of the solution was varied; in acid solution (pH <2·8) the colour was pure yellow, at neutrality red, and in alkaline solutions (pH >10) deep violet (see also Fig. 2). This, together with the general physical and chemical properties (see the Experimental section), suggested that flaviolin was a hydroxylated quinone of strongly acidic character. An electrometric titration revealed the presence of one strongly acidic group (p$K'_a$ 4·7 at 21°) and two much weaker acidic groups (Fig. 2). The ultra-violet absorption spectrum (Fig. 3) revealed strong absorption in the 270—290- and 400—500-mμ regions, a characteristic of, among other compounds, hydroxyanthraquinones and hydroxy-1 : 2- and -1 : 4-naphthaquinones.

Attempts to acetylate flaviolin by most of the normal procedures led to intractable gums. However, acetic anhydride, with perchloric acid as catalyst, gave a good yield of a yellow, beautifully crystalline compound [triacetylflaviolin, $C_{10}H_3O_2(OAc)_3$] from which,

by gentle alkaline hydrolysis, flaviolin could be regenerated—proving that a Thiele reaction had not taken place.

It is well established (Macbeth, Price, and Winzor, *J.*, 1935, 325; Lugg, Macbeth, and Winzor, *J.*, 1937, 1597; Cooke, Macbeth, and Winzor, *J.*, 1939, 878; Arnstein and Cook, *J.*, 1947, 1023) that the ultra-violet absorption spectra of acetoxylated quinones closely approximate to the spectra of the parent unsubstituted quinones.* The absorption spectrum of the triacetate (Fig. 4) indicated it to be, beyond doubt, a derivative of 1 : 4-naphthaquinone (see Friedel and Orchin, " Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons Inc., New York, 1951, graph No. 254) and it showed a close similarity

FIG. 3. FIG. 4.

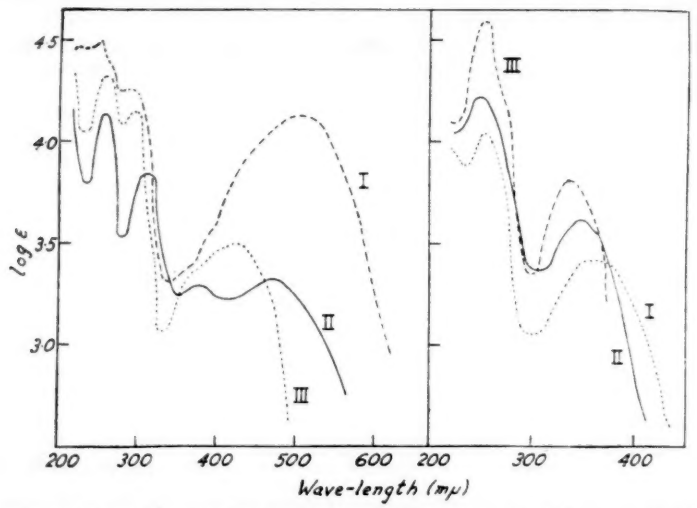
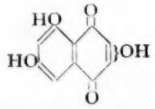
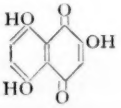



FIG. 3. *Ultra-violet absorption spectra of: I, naphthapurpurin; II, flaviolin; III,* O-*trimethylflaviolin.*

FIG. 4. *Ultra-violet absorption spectra of: I, triacetylnaphthapurpurin; II, triacetylflaviolin; III, diacetylquinizarin.*

to the spectrum of triacetylnaphthapurpurin (Fig. 4 also shows, for comparison, the spectrum of an acetoxylated anthraquinone). Flaviolin is, therefore, a trihydroxy-1 : 4-naphthaquinone.

Flaviolin  Naphthapurpurin 

Methylation of flaviolin by means of methyl sulphate gave a poor yield of the *O*-trimethyl ether, $C_{10}H_3O_2(OMe)_3$, which crystallised in deep-yellow prisms (use of diazomethane led to no pure product), the ultra-violet absorption spectrum of which (Fig. 3) was similar to, but simpler than, that of flaviolin. This ether, when gently warmed with sodium hydroxide solution, dissolved to give a red solution—a reaction undoubtedly due to the production of the sodium salt of a 2(or 3)-hydroxy-dimethoxy-1 : 4-naphthaquinone. The assumption of the presence of a hydroxyl group in the 2(or 3)-position of flaviolin was also necessary to account for the strongly acidic nature of the pigment. It thus appeared that flaviolin contained at least one hydroxyl group in the quinonoid nucleus.

* In this connection it is instructive to note that the effect of an acetoxyl group (in contrast to that of a hydroxyl or methoxyl group) on the oxidation–reduction potential of quinones is very small (see Fieser and Fieser, " Organic Chemistry," 2nd Edn., D. C. Heath & Co., Boston, 1950, p. 755).

Oxidation of triacetylflaviolin with chromic acid in acetic anhydride–acetic acid solution yielded an acidic product which, after gentle hydrolysis to remove the acetyl groups, gave positive colour reactions for 3 : 5-dihydroxyphthalic acid. This hydrolysed oxidation product was, however, impure and could not be crystallised. Its identity was confirmed by conversion into 3 : 5-dimethoxyphthalic anhydride.

Flaviolin is, therefore, 2(or 3) : 5 : 7-trihydroxy-1 : 4-naphthaquinone. Attempts to synthesise the *O*-trimethyl ethers corresponding to the two possible structures are in progress.

So far as we are aware, this is the first recorded instance of the isolation of a 1 : 4-naphthaquinone derivative from a member of the *Aspergillus* genus. Three 1 : 4-naphthaquinone derivatives have been reported as metabolic products of certain *Fusarium* species : javanicin (Arnstein and Cook, *J.*, 1947, 1021), solanione (Weiss and Nord, *Arch. Biochem.*, 1949, **22**, 288), and fusarubin (Ruelius and Gauhe, *Annalen*, 1950, **569**, 38). Solanione and javanicin may be identical.

A 0·1% solution of flaviolin was inactive against a number of *Mycobacteria* (including *M. tuberculosis*). We are indebted to Messrs. Boots Pure Drug Co. Ltd. and Dr. D. A. Peak for this information.

## Experimental

*Isolation of Flaviolin.*—*Aspergillus citricus* (National Collection of Type Cultures, No. 1692, Ac. 72) was kept in sub-culture on Czapek–Dox agar slopes. For production of the pigment the mould was grown in surface culture on either of the two following liquid media : (A) glucose monohydrate (50 g.), ammonium nitrate (2·25 g.), potassium dihydrogen phosphate (0·30 g.), hydrated magnesium sulphate (0·25 g.), and tap-water to 1 l.; (B) glucose monohydrate (5%) and inorganic salts (Czapek–Dox formula) in tap-water. There was little to choose between the two media from the point of view of pigment-production. Flat, round culture-flasks (see *Biochem. J.*, 1944, **38**, 456), each filled with 500 c.c. of medium, were sterilised (10 lb./sq. in. excess steam pressure for 20 min.) and, after having been inoculated with a heavy aqueous spore suspension, were kept at 29° ± 1° for 21—25 days. The substrate (60—70 l. from 140 flasks) was filtered through cotton-wool and concentrated to about 8 l. by passage through a recyclising, climbing-film evaporator. (The mycelium contained no appreciable amount of pigment and was discarded.) The syrupy concentrate was acidified (250 c.c. of concentrated hydrochloric acid) and separated from a dark brown sludge, either by centrifugation in a Sharples "Super Centrifuge," or by decantation after 24 hr. The clear, yellow liquid was extracted with ether. The pigment was removed by shaking the ethereal solution with successive quantities of 20-c.c. portions of a saturated solution of sodium hydrogen carbonate until the aqueous layer no longer became purple. The combined aqueous layers were strongly acidified and extracted with ether. Removal of the ether *in vacuo* yielded 1—2 g. of a dark red paste having a strong odour of valerian. Attempts to purify this crude material by crystallisation were normally unsuccessful. Attempted purification by adsorption chromatography, using a variety of adsorbents, or through the preparation of crystalline derivatives also failed.

In preliminary, small-scale experiments it was shown that the pigment could be separated from impurities by paper chromatography using *n*-butanol and aqueous phosphate buffer solutions. The following $R_F$ values were observed for the pigment :

| pH | 7·0 | 7·5 | 8·0 | 8·5 | 9·0 |
|---|---|---|---|---|---|
| $R_F$ | 0·90 | 0·80 | 0·75 | 0·65 | 0·05 |

For purification of the material on a larger scale the following method was adopted.

Powdered cellulose ("Solka-Floc") was mixed with sufficient aqueous phosphate buffer (0·5M; pH 8·0) to form a fairly liquid paste, separated by filtration, and "dried-off" in warm air. About 0·7 g. of the crude pigment, dissolved in 20 c.c. of butanol (previously equilibrated with the buffer solution), was chromatographed on a column (20 × 3 cm.) of the "buffered cellulose," and the chromatogram was developed with the same solvent. By elution there were obtained, in order : (i) a reddish-brown band (10 c.c.) and (ii) a cherry-red band (30 c.c.). Band (iii) (brown) remained at the top of the column. Fraction (iii) was washed from the cellulose with N-sodium hydroxide solution and the butanol fractions (i) and (ii) were washed with the same reagent. Each alkaline solution was washed exhaustively with ether to remove butanol. After acidification, ether-extraction, and removal of the solvent *in vacuo* fraction (i)

yielded an intractable gum; fraction (ii) gave a bright-red, odourless powder which crystallised from warm dioxan (or dioxan–benzene) in rhombs; fraction (iii) yielded an amorphous, brown substance which showed similar colour reactions (with alkaline reagents) to the product from fraction (ii). Fractions (i) and (iii) were not further investigated.

The yields of crystalline fraction (ii), *flaviolin*, varied from 50 to 250 mg. per batch of 140 culture-flasks. (On one occasion only was it found unnecessary to purify the crude extract by chromatography and direct crystallisation of this crude material yielded 940 mg. of flaviolin.)

*General Properties of Flaviolin.*—The pigment could be crystallised only from hot dioxan or dioxan–benzene; use of other solvents always led to gums. *Flaviolin* formed garnet-red rhombs decomposing at *ca.* 250° [Found (in a sample dried at room temperature *in vacuo* over phosphoric oxide): C, 56·1; H, 4·5; loss at 60° *in vacuo* over $P_2O_5$, 18·7. $C_{10}H_6O_5,\frac{1}{3}H_2O,\frac{1}{2}C_4H_8O_2$ requires C, 56·3; H, 4·2; loss in wt. (for conversion into $C_{10}H_6O_5,\frac{1}{3}H_2O$) 17·2%. Found (in material dried at 60° *in vacuo* over $P_2O_5$): C, 56·5; H, 3·75. Found (in a sample dried at room temperature *in vacuo* over $H_2SO_4$): C, 56·9; H, 3·3; OMe, 0; *C*-Me (Kuhn–Roth), 0. $C_{10}H_6O_5,\frac{1}{3}H_2O$ requires C, 56·6; H, 3·2%]. It was insoluble in light petroleum, sparingly soluble in benzene and water, and readily soluble in ether, ethanol, glacial acetic acid, chloroform, and warm dioxan. In concentrated sulphuric acid it gave an intense bright-red solution. An alkaline aqueous solution (originally deep-violet in colour) became yellow or brown after exposure to the air for some days. The colour of a solution of flaviolin in aqueous sodium hydroxide was destroyed by gently warming the solution with zinc dust and was subsequently restored by shaking the solution with air. Sodium hydrogen carbonate solution completely extracted flaviolin from its ethereal solution. Flaviolin yielded a red-violet ferric reaction (in water) and gave an amorphous precipitate with 2 : 4-dinitrophenylhydrazine solution in aqueous-methanolic sulphuric acid.

*Electrometric Titration of Flaviolin.*—An aqueous solution of the pigment was titrated with 0·01N-sodium hydroxide solution, a glass electrode and a Cambridge pH Meter (Fig. 2) being used.

*Course of Flaviolin Production.*—Some exploratory experiments were made with substrates containing inorganic salts together with 4 or 10% of glucose monohydrate. A substrate containing 6% of glucose monohydrate and inorganic salts as in medium (A) was chosen for detailed examination.

A batch of 500-c.c. conical flasks, each containing 200 c.c. of medium, was inseminated and incubated at 29° ± 1°. At intervals, the substrates from three flasks (chosen at random) were combined and used for the following estimations. (i) The pH was determined electrometrically. (ii) Glucose was determined volumetrically with Pavy's solution. (iii) The concentration of flaviolin was measured thus: 50 c.c. of substrate were acidified to pH 2·0, filtered, and extracted with ether; the ethereal solution was washed once with water, then dried, and the solvent evaporated; the residue was dissolved in ethanol and the intensity of absorption at 265 mμ measured spectroscopically; from a knowledge of the known absorption of pure flaviolin at 265 mμ the concentration of flaviolin in the alcoholic solution was calculated. The results are shown in Fig. 1.

O-*Triacetylflaviolin.*—One drop of aqueous 60% perchloric acid was added to a solution of flaviolin (30 mg.) in acetic anhydride (2 c.c.). The solution became warm and, after having been kept for 1 hr. (without application of heat), it was poured into water. A crystalline product (40 mg.) separated and was repeatedly crystallised from ethyl acetate, to give O-*triacetylflaviolin* (20 mg.) as yellow, slender prisms, m. p. 160—161° [Found: C, 57·4; H, 3·95; Ac, 39·8%; *M* (Rast), 378; *M*, calculated from density of substance (1·390 g./c.c.) and dimensions of unit cell (8·046 × 12·09 × 16·34 Å) and on the assumption of four molecules per unit cell, 333·1. $C_{10}H_3O_5Ac_3$ requires C, 57·8; H, 3·6; Ac, 38·9%; *M*, 332·3]. This material dissolved immediately in cold 2N-sodium hydroxide to give a deep pink colour, which, when the solution was warmed, became intense blue. Acidification and ether-extraction of this solution yielded a substance which was indistinguishable by colour tests (with solutions of sodium acetate, sodium hydrogen carbonate, and sodium hydroxide) and by paper chromatography from flaviolin. That at least one acetoxy-group (probably one in the 2- or 3-position) was readily hydrolysable was shown by the observation that when an ethereal solution of triacetylflaviolin was shaken with a saturated solution of sodium hydrogen carbonate the aqueous layier slowly developed a pink colour which could be discharged by acidification.

Three attempts at reductive acetylation of flaviolin failed. Neither the use of zinc and acetic acid in presence of acetic anhydride nor the use of magnesium, pyridine, and acetic anhydride led to the production of any pure product. In the third attempt triacetylflaviolin (100 mg.) was heated with acetic anhydride (3 c.c.), acetic acid (3 c.c.), and zinc dust (0·5 g.) on a

water-bath for 3 hr. No colour change was observed and triacetylflaviolin (90 mg.) was recovered.

O-*Trimethylflaviolin*.—A solution of flaviolin (75 mg.) and methyl sulphate (1·5 c.c.) in acetone (10 c.c.), with anhydrous potassium carbonate (1·5 g.), was heated under reflux on a water-bath for 8 hr. The mixture was cooled and the acetone largely removed in an air-stream. Addition of water (30 c.c.) led to the separation of an oil which subsequently crystallised. Recrystallisation (to constant m. p.) from ethanol yielded O-*trimethylflaviolin* (6 mg.) as golden-yellow prisms, m. p. 186—187° (decomp.) [Found: C, 62·3; H, 5·2; OMe, 36·4. $C_{10}H_3O_3(OMe)_3$ requires C, 62·9; H, 4·9; OMe, 37·5%]. In a second preparation (similar quantities) the crude material was dissolved in benzene, filtered, and chromatographed on alumina (10 × 1·2 cm.) (Spence, Type "H" which had been "acid washed"). Development with (i) benzene, (ii) benzene containing 10% v/v of ether, and (iii) benzene containing 2% v/v of dry ethanol produced a fast-moving, yellow band which was eluted (a reddish-brown band remained at the top of the column). Removal of the solvents *in vacuo* from the eluate and crystallisation of the residue from aqueous methanol yielded *O*-trimethylflaviolin (10 mg.) as slender, deep-yellow prisms, m. p. 191° (decomp.) (Found: C, 62·9; H, 4·9; OMe, 34·6%). This ether, when warmed with aqueous alcoholic sodium hydroxide, gave a red solution. Acidification and ether-extraction yielded a yellow ethereal solution which, when shaken with the alkaline reagent, immediately produced a red colour in the aqueous phase.

Treatment of flaviolin with an excess of ethereal diazomethane for 2 hr., and removal of the excess of reagent, gave a fluorescent solution (possibly due to the formation of a naphthindazole) which yielded, after evaporation of the ether, a residue from which no pure product was isolatable.

*Degradation of* O-*Triacetylflaviolin*.—To a solution of *O*-triacetylflaviolin (300 mg.) in acetic anhydride (9 c.c.) and acetic acid (5 c.c.) were added 5 c.c. of a solution made by dissolving chromic anhydride (2·5 g.) in water (2 c.c.) and acetic acid (25 c.c.). The mixture was kept at 60—70° for 1 hr., cooled, and diluted with water. The solution was extracted with chloroform (3 × 25 c.c.), and the chloroform extracts (which yielded a small amount of unchanged acetate) were discarded. The aqueous solution was extracted with ether (3 × 50 c.c.). The combined ethereal solutions were washed with water, then dried ($MgSO_4$), and the solvent was removed. The residue (120 mg.) of impure, partly crystalline, diacetoxyphthalic acid was dissolved in 0·2N-sodium hydroxide (17·5 c.c.) and heated on a water-bath for ¾ hr. This solution, after filtration, acidification, exhaustive extraction with ether, and removal of the solvent, yielded a discoloured, partly crystalline product (100 mg.). This material was readily soluble in sodium hydrogen carbonate solution; it gave a reddish-purple ferric reaction and an immediate magenta colour (fading slowly) with an aqueous solution of bleaching powder. This product was undoubtedly impure 3 : 5-dihydroxyphthalic acid but attempts at purification were unsuccessful. It was therefore converted into dimethoxyphthalic anhydride as follows. To a neutralised solution of the acid in water (20 c.c.) was added 35% lead acetate solution (25 c.c.). The washed lead salt was triturated with successive portions of dilute sulphuric acid (10%), and the organic acid recovered (75 mg.) by ether-extraction. To an ethereal solution of the acid was added an excess of ethereal diazomethane. After 16 hr. a negative ferric reaction was obtained and the excess of diazomethane and the ether were removed. The residue was gently heated under reflux with 0·5N-aqueous sodium hydroxide (10 c.c.) for 1 hr. Acidification and ether-extraction yielded crude 3 : 5-dimethoxyphthalic acid (60 mg.). This acid was heated to 170—180° for 15 min. and the product sublimed at 140—150°/0·25 mm. A considerable amount of non-sublimable material remained. The sublimate was purified by two further sublimations, by two crystallisations from benzene–light petroleum (b. p. 60—80°), and finally by sublimation. The product (10 mg.) [Found: C, 57·5; H, 4·3; OMe, 28·9. Calc. for $C_8H_2O_3(OMe)_2$: C, 57·7; H, 3·9; OMe, 29·8%] formed white needles, m. p. 146—147·5° which changed to 146·5—148·5° after admixture with synthetic 3 : 5-dimethoxyphthalic anhydride (Fritsch, *Annalen*, 1897, **296**, 344) of m. p. 147—148·5°.

We thank Professor F. E. King for his interest and encouragement and Dr. S. C. Wallwork for determining the unit-cell dimensions of triacetylflaviolin. One of us (J. C. R.) thanks the Leverhulme Trustees for the award of a Research Fellowship during the tenure of which some of the preliminary work leading to this investigation was performed.

THE UNIVERSITY, NOTTINGHAM. [*Received, June 4th*, 1953.]

## 655. *Structure and Reactivity of Anhydro-sugars. Part I. Branched-chain Sugars. Part I. Action of Diethylmagnesium on Methyl* 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside.*

By A. B. Foster, W. G. Overend, M. Stacey, and G. Vaughan.

The action of diethylmagnesium on methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I) under a variety of conditions has been investigated. The sole product of the reaction in ether is methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-altroside (II) whereas the use of toluene leads to a complex mixture of products. Graded acid hydrolysis of (II) gave methyl 3-deoxy-3-*C*-ethyl-α-D-altroside (IV), the structure of which was proved by oxidation with lead tetra-acetate. Complete acidic hydrolysis of (IV) or (II) afforded a mixture of 3-deoxy-3-*C*-ethyl-D-altrose and -D-altrosan (V and VI), and ionophoretic studies and osazone formation confirmed these structures. The behaviour of the mixture (V–VI) was closely analogous to that of an authentic D-altrose–D-altrosan mixture. A preliminary comment, on the basis of conformational analysis, on the scission of ethylene oxide rings in anhydro-sugars is given.

Although many examples of the interaction of Grignard reagents and molecules containing epoxide rings have been studied (cf. Gaylord and Becker, *Chem. Reviews*, 1951, **49**, 413) investigations with anhydro-sugars of the ethylene oxide type have been limited in scope. In previous publications from this laboratory, Wiggins and his co-workers (Newth, Richards, and Wiggins, *J.*, 1950, 2356; Richards and Wiggins, *J.*, 1953, 2442) have described the action of methyl-, ethyl-, and phenyl-magnesium halides on derivatives of methyl 2 : 3-anhydro-α-D-alloside. In this communication an extension of this work is reported.

As is well known, Grignard reagents may be represented by the equation :

$$2RMgX \rightleftharpoons \begin{bmatrix} \overset{+}{M}gX & R^- \\ \overset{+}{M}gR & X^- \end{bmatrix} \rightleftharpoons MgR_2 + MgX_2$$

The equilibrium lies predominantly to the right, and indeed in certain cases (cf. Huston and Agett, *J. Org. Chem.*, 1941, **6**, 123; Gaylord and Becker, *loc. cit.*) addition of dioxan precipitates the magnesium halide as a complex which can be removed, thereby leaving the dialkylmagnesium as the main component in solution. When methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I) was added to a Grignard reagent (in this case ethylmagnesium iodide) which had been treated with dioxan but without removal of the precipitated complex, reaction occurred exclusively with the dialkylmagnesium in the solution since the sole product was methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-altroside (II). This member of a novel class of branched-chain sugars (cf. Newth, Richards, and Wiggins, *loc. cit.*; see also Hudson, *Adv. Carbohydrate Chem.*, 1949, **4**, 57; Cunningham, Hutchinson, Manson, and Spring, *J.*, 1951, 2299; Bentley, Cunningham, and Spring, *ibid.*, 1951, 2301, for details of other types of branched-chain sugars) was initially isolated by Richards (Ph.D. Thesis, University of Birmingham, 1951) but its structure was not elucidated.

The yields of (II) produced under various reaction conditions are shown in Table 1. Apparently in ether the reaction is relatively simple, and the yield of (II) is then a function of the time of reaction. Anomalous reactions occur, however, since in some cases methyl 4 : 6-*O*-benzylidene-3-deoxy-3-iodo-α-D-altroside (III) was obtained (see Table 1). When the reaction was carried out in tetrahydropyran (II) was not isolated, but (III) was obtained in 88·5% yield indicating that it was the major product of the reaction. The magnesium iodide, although largely precipitated as the dioxan complex, evidently reacts preferentially with (I) under these conditions. The use of toluene as the reaction medium gave a complex variable mixture of products, but in some cases (II) could be isolated in 11·8% yield.

Various pieces of evidence indicated that (II) was correctly designated as methyl

4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-altroside. Although it did not yield a crystalline toluene-*p*-sulphonyl derivative or acetate, a crystalline methanesulphonyl derivative was obtained. Mild hydrolysis of (II) with oxalic acid afforded syrupy methyl 3-deoxy-3-*C*-ethyl-α-D-altroside (IV) which on acetylation gave a syrupy triacetate. The glycoside (IV) in dry benzene solution was resistant to oxidation by lead tetra-acetate

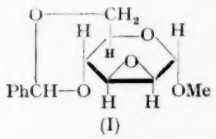
TABLE 1. *Reaction of methyl* 2 : 3-*anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside* (I) *with diethylmagnesium, in the presence of the precipitated magnesium iodide–dioxan complex.*

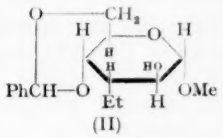
| Solvent | Duration of reaction, hr. | Temp., °C | Wt. of (I) recovered, g. | Wt. of (II) isolated, g. | Wt. of (III) isolated, g. | % Yield of (II) * |
|---|---|---|---|---|---|---|
| Ether ..... | 8—9 | 70 | 0·839 | 0·325 | — | 67·3 |
| Ether ..... | 12 | 70 | 0·686 | 0·562 | — | 90·6 |
| Ether ..... | 24 | 70 | 0·457 | 0·724 | — | 83·5 |
| Ether ..... | 48 | 70 | 0·810 | trace | 0·517 | — † |
| Tetrahydropyran | 9 | 81 | 0·890 | — | 0·560 | — |
| Toluene ..... | 8 | 112 | — | 0·174 | — | 11·8 ‡ |

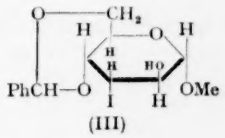
The amount of (I) used in each case was 1·32 g. (see Experimental section).

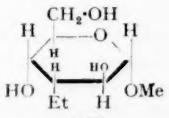
* Based on the amount of (I) not recovered.
† Reaction mixture was set aside at room temperature for 24 hr. before being heated.
‡ Three unidentified syrupy products were also obtained.

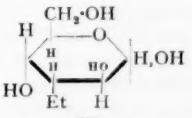
which clearly indicated that the *C*-ethyl group was located at $C_{(3)}$. More drastic treatment of (II) with oxalic acid removed both benzylidene and glycosidic groups and gave a syrupy product which was only weakly reducing towards Fehling's solution. This property

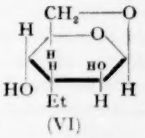

(I)


(II)


(III)


(IV)


(V)


(VI)

together with the elemental analysis suggested that the product was a mixture of the free sugar and an anhydro-derivative, with the latter predominating. This evidence supports the allocation of the D-altrose configuration to (II), since it is well known that acidic hydrolysis of methyl α-D-altroside or its derivatives leads to the formation of a mixture of the free sugar and its 1 : 6-anhydro-derivative (altrosan) (Newth and Wiggins, *J.*, 1950, 351; Hudson and Richtmyer, *J. Amer. Chem. Soc.*, 1935, **57**, 1716). If, as is exceedingly probable, the scission of the epoxide ring in (I), by diethylmagnesium in ether, involves Walden inversion at the carbon atom where the ethyl group is introduced (cf. Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37) then of the two products theoretically derivable that with the new substituent at $C_{(3)}$ would be expected to have the D-altrose configuration. The weakly reducing product isolated after complete hydrolysis of (II) is therefore most probably a mixture of 3-deoxy-3-*C*-ethyl-αβ-D-altrose (V) and its 1 : 6-anhydro-derivative (VI).

Treatment of the mixture (V–VI) with 2 : 4-dinitrophenylhydrazine (3 mol.) under mild conditions gave a low yield (18%) of 3-deoxy-3-*C*-ethyl-D-altrose 2 : 4-dinitrophenylhydrazone. With 3 mol. of the 2 : 4-dinitrophenylhydrazine under more drastic conditions an osazone was obtained in 35% yield. The low yields are in agreement with the small amount of the D-altrose derivative in the mixture (see below), since molecules of the D-altrosan type are known to be very stable (Peat, *loc. cit.*). It is extremely unlikely that osazone formation would have occurred had the *C*-ethyl group been located at $C_{(2)}$. In

model experiments it was shown that whereas 3-deoxy-D-mannose formed an osazone, 2-deoxy-D-glucose underwent decomposition and yielded only tarry products.

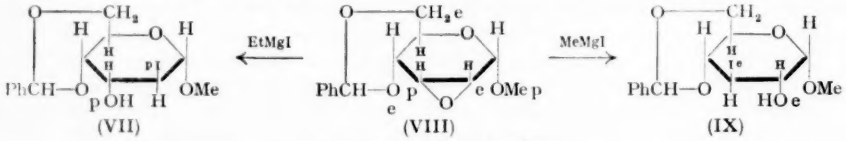
Further support for the allocation of the D-altrose configuration to (II) follows from the ionophoretic behaviour of the mixture (V–VI). The favoured interaction of hydroxylated pyran structures with borate ions at pH 10, under the conditions of filter-paper ionophoresis previously described (Foster, *Chem. and Ind.*, 1952, 1050), involves vicinal *cis*-hydroxyl groups (Foster, *J.*, 1953, 982, and unpublished results). Such a structural feature is present in the β-form of (V) and absent in the altrosan structure (VI), and so (VI) would be expected to have zero ionophoretic migration ($M_G$ value; Foster, *loc. cit.*; Foster and Stacey, *J. Appl. Chem.*, 1953, **3**, 19). The $M_G$ values recorded in Table 2 demonstrate the closely similar and expected ionophoretic behaviour of the mixture (V–VI) to that of a 3-deoxy-3-iodo-αβ-D-altrose–altrosan mixture of proved structure (Richards, *loc. cit.*). The important rôle of the hydroxyl group at $C_{(2)}$ in the interaction of reducing (pyranose and furanose) sugars with borate ions enables the location of a substituent at $C_{(2)}$ to be easily determined (Foster, *loc. cit.*). The $M_G$ value of the altrose component of the mixture (V–VI) in comparison with the various 2- and 3-substituted derivatives listed in Table 2 is clear evidence for the absence of a substituent at $C_{(2)}$ in (V).

TABLE 2. $M_G$ *values of some carbohydrate derivatives.*

| Derivative | $M_G$ | Derivative | $M_G$ |
|---|---|---|---|
| 3-Deoxy-3-iodo-D-altrose–altrosan ... | 0·00, 0·73 | 2-Deoxy-D-glucose ..... | 0·24 |
| 3-Deoxy-3-*C*-ethyl-D-altrose–altrosan | 0·00, 0·73 | 2-Methyl-D-glucose ..... | 0·24 * |
| 2-Methyl-D-galactose ..... | 0·32 * | 3-Methyl-D-glucose ..... | 0·78 |
| 2-Deoxy-D-galactose ..... | 0·37 * | 3-Deoxy-D-mannose ..... | 0·76 |

* Values described by Foster (*J.*, 1953, 982).

Although numerous examples of the scission of epoxide rings in ethylene oxide anhydro-sugar derivatives, under the influence of a variety of reagents, have been recorded, the underlying principles governing the manner of opening of the epoxide rings have not been fully elucidated. Mills (Addendum to Newth and Homer, *J.*, 1953, 989) has suggested that sugar epoxides may behave in a manner analogous to steroid epoxides in undergoing scission to products with the new substituents in polar positions. If the anhydro-sugar is able to oscillate freely between its possible conformations then cleavage of the epoxide ring will give a mixture of the two possible isomeric products in more or less equal amounts. Any excess of one isomer over the other will depend on the general symmetry of the particular sugar. However the presence for example of a 4 : 6-*O*-benzylidene residue will effectively stabilise one particular conformation and on scission of the epoxide ring one of the two possible isomeric products will predominate according to the conformational requirements.




e = equatorial; p = polar.

There are other factors however which cannot be neglected. This is effectively demonstrated by the action of Grignard reagents on certain 2 : 3-anhydro-sugars. As stated, the action of diethylmagnesium in ether on (I) leads exclusively to the formation of (II). Since the benzylidene residue in (I) is best accommodated when the hydroxyl and hydroxymethyl groups at $C_{(4)}$ and $C_{(5)}$ respectively are equatorially situated, the sole product (II) subsequently isolated has the groups at $C_{(2)}$ and $C_{(3)}$ in polar positions. This result is in agreement with Mills's suggestion (*loc. cit.*). The action of ethylmagnesium iodide in tetrahydropyran on methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (VIII) (Richards and Wiggins, *loc. cit.*) also follows the predicted course in yielding as sole product methyl 4 : 6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altroside (VII). On the other hand methylmagnesium iodide in a similar reaction (Newth, Richards, and Wiggins, *loc. cit.*) gives as the sole product methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-iodo-α-D-glucoside (IX) with the

new substituents both equatorial. It is significant that the course of the reaction is completely altered and not partly so as might normally be expected following the use of such apparently closely related reagents as methyl- and ethyl-magnesium iodide. A full analysis of the reaction of sugar epoxides will be published later.

## Experimental

*Reaction of Methyl* 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside with Diethylmagnesium.*—(a) *In ether at* 70°. To an ethereal solution of ethylmagnesium iodide [from ethyl iodide (15·6 g.; 8·08 ml.), magnesium turnings (2·4 g.), and ether (50 ml.)], in an open Carius tube, dioxan (12 ml.) was added at room temperature with vigorous stirring. To the resultant white paste was added a solution of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (1·32 g.) in ether (50 ml.) containing dioxan (2 ml.; to facilitate dissolution); meanwhile stirring was continued. The white suspension was heated under reflux for 1 hr., and after being cooled with liquid air, the Carius tube was sealed off. The tube was then heated at 70° for 8 hr. [In subsequent experiments varying periods of heating were used. For the effects see Table 1.] After cooling, the contents of the tube were poured into water (200—300 ml.), and the mixture worked up in the usual manner to give a white solid, a solution of which, in ether–light petroleum (b. p. 60—80°)–chloroform (2 : 1 : 2; v/v/v; 25 ml.), was passed through alumina (30 × 1 cm.). Elution with ether–light petroleum (b. p. 60—80°) (2 : 1; v/v; 300 ml.) and concentration of the eluate yielded starting material (0·839 g.). Concentration of a subsequent chloroform eluate (200 ml.), decolorisation of the pale brown syrupy residue with activated charcoal in methanol, and evaporation of the solvent afforded a syrup which rapidly crystallised. The product was extracted with hot light petroleum (b. p. 60—80°) and on cooling the extract deposited methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-hexoside (altroside) (*A*) (0·325 g.) as white needles, m. p. 97—98°, $[\alpha]_D^{16}$ +113° (*c*, 0·91 in $CHCl_3$) (Found : C, 65·0; H, 7·5. Calc. for $C_{16}H_{22}O_5$ : C, 65·3; H, 7·5%). [Richards, Ph.D. Thesis, Univ. of Birmingham, 1951, reports m. p. 97—98°, $[\alpha]_D^{23}$ +113·5° (*c*, 0·82 in chloroform).]

(b) *In tetrahydropyran.* Diethylmagnesium was prepared as described above. The ether was removed by distillation and immediately replaced by tetrahydropyran (50 ml.). Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (1·32 g.) dissolved in tetrahydropyran (100 ml.) was added and the mixture stirred and heated under reflux for 9 hr. It was set aside at room temperature overnight and then poured into ice–water (300 ml.) and worked up in the usual manner to give a yellow solid. Extraction of this material with ether–light petroleum (2 : 1; v/v; 15 ml.) left starting material (0·32 g.). The soluble fraction (1·23 g.) was passed through alumina (30 × 1 cm.), wet packed in ether–light petroleum (b. p. 60—80°; 2 : 1; v/v). Elution with ether–light petroleum (b. p. 60—80°; 2 : 1; v/v) afforded more starting material (0·57 g.). Elution with chloroform and concentration of the eluate yielded a yellow syrup (0·56 g.) which was crystallised by trituration with methanol. Recrystallisation from methanol gave methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-iodo-α-D-altroside (0·4 g.), m. p. 162·5—163° (undepressed on admixture with an authentic specimen), $[\alpha]_D^{20}$ +114° (*c*, 1·01 in $CHCl_3$) (Found : C, 42·9; H, 4·6. Calc. for $C_{14}H_{17}O_5I$ : C, 42·85, H, 4·4%). [Richards, *loc. cit.*, reports m. p. 163—163·5°, $[\alpha]_D^{22}$ +111·4° (*c*, 4·19 in $CHCl_3$).] No other compound was isolable from the mother liquors.

(c) *In toluene.* Dioxan (12·0 ml.) was added with vigorous stirring to an ethereal solution of ethylmagnesium iodide [from magnesium (2·4 g.) and ethyl iodide (8·08 ml.)]. Ether was removed carefully by slow distillation and was simultaneously replaced by dry tolueue (100 ml.). Thereafter the solution was cooled and the methyl anhydro-D-mannoside derivative (1·32 g.) in dry toluene (100 ml.) added. The mixture was stirred continuously and heated under reflux for 8 hr. Hydrolysis followed by extraction of the reaction mixture as previously described afforded a pale yellow syrup, which was dissolved in the minimum of ether–light petroleum (b. p. 60—80°; 2 : 1; v/v) and chromatographically separated on alumina (30 × 1·5 cm.); four fractions were obtained :

(i) Elution with ether–light petroleum (b. p. 60—80°)–chloroform (2 : 1 : 2; v/v/v; 200 ml.) gave methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-hexoside (*A*), m. p. 97°, $[\alpha]_D^{19}$ +113° (*c*, 1·5 in $CHCl_3$). Fraction (ii), obtained by elution with ether (100 ml.), was a pale yellow unidentified syrup (0·102 g.) which failed to crystallise. Fraction (iii) (0·192 g.) was obtained by subsequent elution with chloroform (200 ml.). This was also an unidentified syrup. (iv) Finally, elution with methanol (100 ml.) gave syrup (1·154 g.) (Found : C, 67·2; H, 9·0%).

*Derivatives of Methyl* 4 : 6-O-*Benzylidene*-3-*deoxy*-3-C-*ethyl*-α-D-*hexoside* (A).—(a) 2-O-

*Toluene-*p*-sulphonyl derivative.* Methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-hexoside (0·147 g.) in dry pyridine (3 ml.) was treated with toluene-*p*-sulphonyl chloride (0·105 g., 1·15 mol.). The 2-O-*toluene-*p*-sulphonyl* derivative (0·15 g., 67% of theory) was obtained as a syrup, $n_D^{19}$ 1·5000, $[\alpha]_D^{19}$ +75° (*c*, 0·8 in $CHCl_3$) (Found: C, 61·7; H, 6·6; S, 7·3. $C_{23}H_{28}O_7S$ requires C, 61·5; H, 6·3; S, 7·2%).

(b) 2-O-*Methanesulphonyl derivative.* Likewise the 2-O-*methanesulphonyl* derivative was prepared; it had m. p. 136—137° (after recrystallisation from ethanol), $[\alpha]_D^{19}$ +61·5° (*c*, 3·26 in $CHCl_3$) (Found: C, 55·1; H, 6·8; S, 8·6. $C_{17}H_{24}O_7S$ requires C, 54·9; H, 6·5; S, 8·6%).

*Hydrolysis of Methyl* 4 : 6-O-*Benzylidene-*3*-deoxy-*3*-C-ethyl-*α*-D-hexoside* (A).—(a) *Partial acidic hydrolysis.* Methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-hexoside (0·4 g.) was dissolved in acetone (50 ml.), and a solution of oxalic acid (0·7 g. of hydrate) in water (2·5 ml.) was added. The mixture was heated under reflux and the ensuing hydrolysis was followed polarimetrically. It was complete in 400 min.

The solution was diluted with water, made slightly alkaline with aqueous barium hydroxide and then neutralised with solid carbon dioxide. After filtration, the solution was concentrated to a syrupy residue. Extraction with ethyl acetate followed by evaporation of the extracts afforded a pale yellow non-reducing syrup (B) (0·24 g.). Acetylation by use of acetic anhydride in pyridine gave syrupy methyl 2 : 4 : 6-tri-*O*-acetyl-3-deoxy-3-*C*-ethyl-α-D-hexoside, $[\alpha]_D^{20}$ −15·0° (*c*, 1·2 in $CHCl_3$) (Found: C, 54·3; H, 7·1. Calc. for $C_{15}H_{24}O_8$: C, 54·2; H, 7·3%) (Richards, *loc. cit.*, described this compound as amorphous, $[\alpha]_D^{16}$ −14·1°).

The syrupy product (B) (20 mg.) was dissolved in boiling dry benzene (49 ml.), and after cooling, a standard solution of lead tetra-acetate [50 ml. of a solution prepared by dissolving lead tetra-acetate (7·25 g.) in dry benzene (250 ml.)] was added and the volume was made up to 100 ml. The solution was placed in a thermostat at 25°, and aliquots (10 ml.) were removed at intervals and the uptake of oxidant determined titrimetrically. Results obtained were as follows:

| Time (days) ..... | 1 | 2·5 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| Uptake of $Pb(OAc)_4$ (mol.) ..... | 0·013 | 0·036 | 0·043 | 0·050 | 0·055 | 0·060 |

(b) *Complete acidic hydrolysis.* Methyl 4 : 6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-hexoside (altroside) (0·81 g.) dissolved in oxalic acid solution [81 ml. of a solution prepared by dissolving oxalic acid hydrate (9·0 g.) in water (30 ml.) and acetone (270 ml.)] was heated under reflux for 8·6 hr. The ensuing hydrolysis was followed polarimetrically and was complete in 8 hr. The solution was neutralised as previously described, filtered, and concentrated to a syrup. Water was distilled several times over this material to remove benzaldehyde and thereafter the syrup was extracted with ethyl acetate (3 × 20 ml.). Evaporation of the extract afforded a syrup (0·45 g.) which after decolorisation (activated charcoal) in ethanolic solution was slightly reducing, $[\alpha]_D^{20}$ +65° (*c*, 1·0 in methanol) (Found: C, 55·1; H, 8·4. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3. $C_8H_{14}O_4$ requires C, 55·2; H, 8·05%). It seemed that the product was a mixture of a 3-deoxy-3-*C*-ethyl-D-hexose (altrose) and a 3-deoxy-3-*C*-ethyl-D-hexosan (altrosan). The Keller–Kiliani test was negative. This product (0·14 g.), dissolved in a small amount of water, was treated with a solution of 2 : 4-dinitrophenylhydrazine [prepared by dissolving the hydrazine derivative (0·45 g.) in glacial acetic acid (10 ml.), water (10 ml.), and methanol (5 ml.) and filtering the solution] at 100° for 1 hr., and the reddish-brown solid (0·05 g.; 18%) was removed by filtration while the solution was still hot and was washed with methanol. Recrystallisation from a large volume of methanol gave 3-*deoxy*-3-C-*ethyl*-D-*hexose* (*altrose*) 2 : 4-*dinitrophenylhydrazone* as orange-red microcrystals, m. p. 218° (Found: C, 45·6; H, 5·6; N, 15·3. $C_{14}H_{20}O_8N_4$ requires, C, 45·2; H, 5·4; N, 15·1%).

*Formation of Osazones with* 2 : 4-*Dinitrophenylhydrazine.*—The general method adopted was to treat an aqueous solution of the sugar (1 mol.) with 2 : 4-dinitrophenylhydrazine (3 mol.) dissolved in 60 times its weight of 2N-hydrochloric acid containing 1% of methanol, and to heat the mixture at 100° for 6 hr. The flocculent product was filtered off at 80°, and was washed successively with 2N-hydrochloric acid, water, and methanol. In this way 3-*deoxy*-D-*mannose* 2 : 4-*dinitrophenylosazone* was prepared in microcrystalline form (recrystallisation from ethyl acetate and ethanol), m. p. 205° (with decomp.) (Found: N, 21·7. $C_{18}H_{18}O_{11}N_8$ requires, N, 21·5%). 2-Deoxy-D-glucose when subjected to the above procedure rapidly decomposed with the formation of tarry products.

The hydrolysate of compound (A) yielded an orange-coloured solid, which after recrystallisation from absolute ethanol had m. p. 196° (Found: N, 20·4. $C_{20}H_{22}O_{11}N_8$ requires N, 20·4%). It was most probably 3-*deoxy*-3-C-*ethyl*-D-*altrose* 2 : 4-*dinitrophenylosazone*.

*Ionophoretic Experiments.*—The experiments were performed in the apparatus and by the technique described by Foster (*Chem. and Ind.*, 1952, 1050). Whatman No. 3 paper was used throughout, and the buffer employed was 0·2M-sodium borate (pH 10). The duration of the ionophoreses was 1·5 hr. in all cases under an applied potential of 900 v, which gave a final current of 32—35 ma. Detection of the sugar derivatives on the ionophoretogram was achieved by use of aniline hydrogen phthalate (Partridge, *Nature*, 1948, **164**, 443). The sugars employed are listed in Table 2, and in each case 40—60 $\gamma$ were placed on the ionophoretogram.

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# NOTES.

## 656. α-*Methyl-lævulic Acid.*

By E. A. BRAUDE and C. J. TIMMONS.

α-METHYL-LÆVULIC ACID (III) has been synthesised by a number of methods (see, *e.g.*, Bischoff, *Annalen*, 1881, **206**, 320; Fittig and Gottstein, *ibid.*, 1883, **216**, 31; Béhal, *Bull. Soc. chim.*, 1901, **25**, 245; Agello and Casmano, *Gazzetta*, 1940, **70**, 755; Nazarov and Elizarova, *Izvest. Akad. Nauk U.S.S.R.*; *Otdel. Khim. Nauk*, 1951, 295), none of which is very satisfactory. A more convenient route, readily adaptable to large-scale preparations, consists in the addition of hydrogen cyanide to pent-3-en-2-one (I) to give α-methyl-lævulonitrile (II), followed by alkaline hydrolysis. The nitrile was characterised by the semicarbazone, 2 : 4-dinitrophenylhydrazone, and an unstable phenylhydrazone. The

$$\underset{(I)}{Me\cdot CO\cdot CH{:}CHMe} \longrightarrow \underset{(II)}{Me\cdot CO\cdot CH_2\cdot CHMe\cdot CN} \longrightarrow \underset{(III)}{Me\cdot CO\cdot CH_2\cdot CHMe\cdot CO_2H}$$

formation of $\gamma$-keto-nitriles from $\alpha\beta$-ethylenic ketones, presumably by 1 : 4-addition, has been observed in other cases (cf. Lapworth, *J.*, 1904, **85**, 1218; Maire, *Bull. Soc. chim.*, 1908, **3**, 284; Huan, *ibid.*, 1938, **5**, 1341), though cyanohydrins are obtainable at low temperatures (Marvel and Brace, *J. Amer. Chem. Soc.*, 1948, **70**, 1775; Leupold and Vollmann, U.S.P. 2,166,600; Dykstra, U.S.P. 2,188,340; Hansley and Bristol, U.S.P. 2,456,188). The ultra-violet light absorption of the α-methyl-lævulic acid and its derivatives confirms the accepted open-chain structures (III).

*Experimental.*—M. p.s marked (K) were determined on a Kofler micro-melting point block and are corrected. Other m. p.s are uncorrected.

α-*Methyl-lævulonitrile.* A mixture of pent-3-en-2-one (84 g.), anhydrous hydrogen cyanide (42 g.), and potassium cyanide (1 g.) was kept for 15 hr. at room temperature, then neutralised with phosphoric acid and distilled, giving the *nitrile* (40 g.) as a colourless liquid, b. p. 68°/1 mm., $n_D^{16}$ 1·4288, $\lambda_{infl}$ 2600 Å (ε 90) in hexane (Found : C, 64·6; H, 8·2; N, 12·5. $C_6H_9ON$ requires C, 64·8; H, 8·2; N, 12·6%). The *semicarbazone* separated from ethanol as colourless plates, m. p. 156° (K), $\lambda_{max.}$ 2260° Å (ε 11,000) in EtOH (Found : C, 50·6; H, 7·4; N, 33·5. $C_7H_{12}ON_4$ requires C, 50·0; H, 7·2; N, 33·3%). The phenylhydrazone crystallised from aqueous methanol and had m. p. 76—78°, but was unstable and liquefied on being kept. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol–ethyl acetate in yellow needles, m. p. 130—131°, $\lambda_{max.}$ 3560 Å (ε 23,000) in $CHCl_3$ (Found : C, 49·8; H, 4·7; N, 24·7. $C_{12}H_{13}O_4N_5$ requires C, 49·5; H, 4·5; N, 24·1%).

α-*Methyl-lævulic acid.* (*a*) The above nitrile (40 g.) was heated under reflux with aqueous sodium hydroxide (20%, 200 ml.) for 20 min. After cooling, the solution was acidified with hydrochloric acid and then extracted with ether. Distillation of the ethereal extract gave α-methyl-lævulic acid as a colourless oil (20 g.), b. p. 103°/1 mm., $n_D^{19}$ 1·4388, $\lambda_{infl.}$ 2790 Å (ε 22) in EtOH (Found : C, 55·4; H, 7·6. Calc. for $C_6H_{10}O_3$ : C, 55·4; H, 7·7%) (Nazarov and Elizarova, *loc. cit.*, give b. p. 120—122°/4 mm., $n_D^{22}$ 1·4400). The overall yield from the pentenone was 16%, but this is undoubtedly capable of improvement. The semicarbazone

separated from ethanol in needles, m. p. 182—183° undepressed on admixture with the sample described below, $\lambda_{max.}$ 2250 Å (ε 12,000) in EtOH (Found: C, 45·2; H, 7·2; N, 23·0. Calc. for $C_7H_{13}O_3N_3$: C, 44·9; H, 7·0; N, 22·5%) (Béhal, *loc. cit.*, gives m. p. 191—192°; Michael and Ross, *J. Amer. Chem. Soc.*, 1931, **53**, 2394, give m. p. 191°; Nazarov and Elizarova give m. p. 177—178°). The phenylhydrazone crystallised from water and had m. p. 130—132°; it rapidly decomposed on being kept (Pieroni and Veremscenco, *Gazzetta*, 1926, **56**, 469, give m. p. 134—135°; Ajello and Casmano, *loc. cit.*, give m. p. 130°).

(*b*) An authentic sample of the acid was prepared in the following manner (cf. Conrad, *Annalen*, 1877, **188**, 226; Bischoff, *loc. cit.*). Ethyl α-bromopropionate (56 g.) was added to a solution of ethyl acetoacetate (37 g.) and sodium (8 g.) in ethanol and the mixture was heated under reflux for 12 hr. after which it was neutral to litmus paper. Distillation gave the diethyl 1-acetyl-2-methylsuccinate (16 g.), b. p. 86—87°/0·4 mm., $n_D^{21}$ 1·4398, $\lambda_{max.}$ 2250 Å (ε 2400) in EtOH (Found: C, 57·8; H, 7·7. Calc. for $C_{11}H_{18}O_5$: C, 57·4; H, 7·9%), which did not form a 2 : 4-dinitrophenylhydrazone under the usual conditions and appears to exist predominantly in the enol form under these conditions. The ester was hydrolysed with aqueous sodium hydroxide (5%; 70 ml.) and then heated with 50% (v/v) sulphuric acid (30 ml.), and the products were isolated with ether. Fractionation gave α-methyl-lævulic acid (4 g.; overall yield from ethyl bromopropionate, 10%), b. p. 98°/0·3 mm. [semicarbazone, m. p. 180—182° (K) from ethanol], and 3-carboxy-2 : 4-dimethylbut-3-enolide (4-hydroxypent-3-ene-2 : 3-dicarboxylic acid 2 → 4-lactone) (1·2 g.) which crystallised from chloroform in prisms, m. p. 179—180° (K), $\lambda_{max.}$ 2270 Å (ε 27,000) in EtOH (Found: C, 53·7; H, 5·3%; equiv., 155. Calc. for $C_7H_8O_4$: C, 53·8; H, 5·2%; equiv., 156). Sprankling (*J.*, 1897, 1159) gives m. p. 176°; Küster, Maurer and Palm (*Ber.*, 1926, **59**, 1020) give m. p. 175°. The lactone gives a positive Légal test and reduces Tollens's reagent, but not ammoniacal silver nitrate.

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## 657. *The Preparation and Properties of* cis- *and* trans-*Pent-2-en-4-yne.*

By J. L. H. Allan and M. C. Whiting.

The simple hydrocarbon, pent-2-en-4-yne, is of interest in that its employment in mixed-coupling reactions with other acetylenic compounds has proved, in the hands of Sörensen and his collaborators, to be useful in the synthesis of naturally occurring compounds containing the terminal grouping $CH_3{\cdot}CH{:}CH{\cdot}[C{:}C]_2{\cdot}$. It was first prepared in 1948 by the action of potassium hydroxide on 1-methylbut-3-ynyl toluene-*p*-sulphonate as an apparently homogeneous liquid, b. p. 46—48°; this method was communicated to Prof. Sörensen before publication (Eglinton and Whiting, *J.*, 1950, 3650), who found evidence (Sörensen *et al.*, *Acta Chem. Scand.*, 1951, **5**, 1244) that the hydrocarbon was a mixture of isomers, though the separation achieved was by no means complete.

We now describe the separation of this hydrocarbon into two pure steroisomers. The boiling points and refractive indices of the fractions obtained (see p. 3316) constitute good evidence of separation into two entities, though one of these might in principle be an azeotrope. For this reason infra-red spectra (see Table) were examined. The strongest band of the lower-boiling fraction, at 723 cm.$^{-1}$, is absent from that of the fraction, b. p. 52·2°; it is, moreover, in a region (675—729 cm.$^{-1}$) characteristic for simple *cis*-1 : 2-disubstituted ethylenes (Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1; McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318). Accordingly the higher-boiling fraction is the pure *trans*-form, a conclusion in agreement with its strong band at 956 cm.$^{-1}$ (cf. the similar strong bands in simple *trans*-1 : 2-disubstituted ethylenes at 964—979 cm.$^{-1}$; *idem*, *locc. cit.*). The lower-boiling fraction also had a strong band at about the same frequency, however, in addition to that at 723 cm.$^{-1}$, and it was considered just possible that this was an azeotrope of the two forms; against this view was the fact that fairly strong bands at 1742, 1381, 1287, and, especially, 1027 cm.$^{-1}$, present in the spectrum of the higher-boiling fraction, were absent from that of the substance, b. p. 44·6°. The latter was therefore converted

into the mercury derivative (method of Johnson and McEwen, *J. Amer. Chem. Soc.*, 1926, **48**, 469), m. p. 48°, which after repeated crystallisation was decomposed, giving a hydrocarbon the infra-red spectrum of which was virtually unaltered. It therefore seems certain that the strong band at 958 cm.$^{-1}$ is properly attributed to *cis*-pent-2-en-4-yne and that the lower-boiling fraction was in fact this hydrocarbon in a state of high purity.

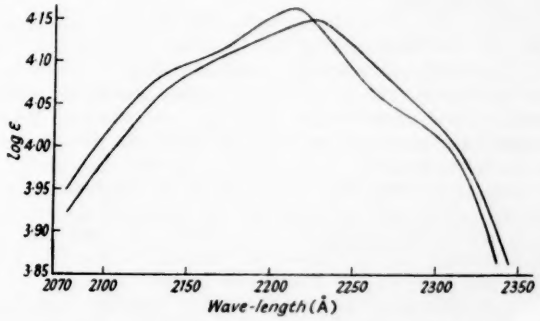
While no attempt has been made to analyse quantitatively the intermediate fractions

*Infra-red absorption maxima for* cis- *and* trans-*pent-2-en-4-yne.*

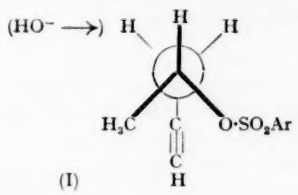
| *cis* | | | | *trans* | | | |
|---|---|---|---|---|---|---|---|
| $\nu$ (cm.$^{-1}$) | $\varepsilon$ † | $\nu$ (cm.$^{-1}$) | $\varepsilon$ † | $\nu$ (cm.$^{-1}$) | $\varepsilon$ † | $\nu$ (cm.$^{-1}$) | $\varepsilon$ † |
| 3390 | 67 * | 1623 | 7 | 3390 | 64 * | 1634 | 8 |
| 3025 | 13 | 1444 | 24 | 3015 | 13 | 1447 | 26 |
| 2955 | 9 | 1425 | 13 | 2950 | 14 | 1381 | 8 |
| 2930 | 13 | 1366 | 21 | 2935 | 14 | 1287 | 8 |
| 2912 | 13 | 1227 | 13 | 2912 | 16 | 1221 | 11 |
| 2850 | 7 | 1035 | 0·2 | 2850 | 8 | 1027 | 24 |
| 2108 | 5 | 958 | 49 * | 2112 | 8 | 956 | 138 * |
| 1995 | 1·8 | 891 | 6 | 1998 | 0·6 | 900 | 14 |
| 1764 | 1·3 | 787 | 3·5 | 1823 | 1·6 | | |
| 1679 | 4·5 | 723 | 114 * | 1742 | 3·5 | | |

* 0·05-cm. cell, 1% solution in $CS_2$.

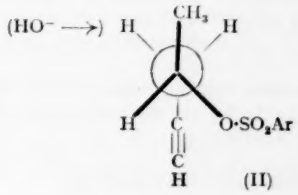
† These values are only approximate. They refer to the neat liquid in a 0·0025-cm. cell, except for those marked *.




obtained in the distillation, it is clear that the crude pent-2-en-4-yne contains about 60—65% of the *cis*-form, a fact for which only one explanation suggests itself. Apparently the conformation (I) is *either* (*a*) more probable, or (*b*) better able to react with $OH^-$, than (II) (the molecules are viewed along the line of the C–C bond which becomes ethylenic). There seems to be no foundation for hypothesis (*b*), but hypothesis (*a*) is supported by the probability of weak electrostatic interaction between alkyl groups and unsaturated systems in their vicinity, suggested by Braude and Coles (*J.*, 1951, 2085) in a less favourable case involving methyl and vinyl groups.




(I)




(II)

The ultra-violet absorption spectra of the two isomeric hydrocarbons are illustrated; the sharper fine structure in that of the *cis*-form is noteworthy, and may be tentatively ascribed to the increased rigidity resulting from the quasi-cyclic structure implied by attraction between the methyl and ethynyl groups.

*Experimental.—Pent-2-en-4-yne.* The hydrocarbon was prepared by Eglinton and Whiting's method (*loc. cit.*) from 1-methylbut-3-ynyl toluene-*p*-sulphonate (654 g.), and the crude dried product (170 g.) was used directly for fractionation. "Teepol," used in this experiment, is an alkali-stable proprietary detergent. In several runs yields of 93—97% were obtained.

*Separation of* cis- *and* trans-*isomers.* The apparatus, supplied by Griffin and Tatlock, Ltd., consists of a vacuum-jacketed glass column (45·7 × 1·7 cm.), packed with gauze rings (Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 88; 1949, **68**, 119) and fitted with a total-condensation still-head and automatic control of take-off. The electrically heated boiler incorporates a device for measuring the boil-up rate. From published data the efficiency should be at least 60 theoretical plates at a reflux ratio of 60 : 1.

| Fraction no. | B. p. | Wt. (g.) | $n_D^{16.5}$ * | Fraction no. | B. p. | Wt. (g.) | $n_D^{16.5}$ * |
|---|---|---|---|---|---|---|---|
| 1 | 43·8—44·5 | 7·7 | 1·4361 | 13 | 49·3—51·3 | 5·80 | 1·4406 |
| 2—10 | 44·5—44·6 | 61·8 | 1·4377 ± 0·0001 | 14 | 51·3—52·0 | 6·70 | 1·4408 |
| 11 | 44·6—45·0 | 7·05 | 1·4381 | 15—20 | 52·0—52·2 | 48·65 | 1·4407—1·4408 |
| 12 | 45·0—49·3 | 9·65 | 1·4399 | | | | |

* Determined after *ca.* 24 hr. at 0°. The liquid had therefore undergone slight oxidation and/or polymerisation. For accurate values, see text.

The boiler charge was pent-2-en-4-yne isomers (160 g.), with benzene (25 c.c.) as chaser. After pre-flooding, the column was left on total reflux for 4½ hr. before the collection of fractions at a rate of 5·8 c.c./hr.; the boil-up rate remained at 360 c.c./hr. The atmospheric pressure remained almost constant throughout the distillation (766·7 ± 0·2 mm.). The Table lists detailed results. Fractions 6 and 18 were used for light-absorption determinations and the preparation of mercury derivatives.

*Di*-(cis-*pent*-2-*en*-4-*ynyl*)*mercury*. *cis*-Pent-2-en-4-yne (5·75 g.) in ethanol (20 vol.) was added during 30 min., at <0° with cooling and stirring, to a solution (124 c.c.) made by dissolving mercuric chloride (66 g.) and potassium iodide (163 g.) in water (163 c.c.) and adding 10% aqueous sodium hydroxide (125 c.c.). After further 5 minutes' stirring the crystalline precipitate was filtered off and washed with 50% aqueous ethanol. Recrystallisation from ethanol gave *di*-(cis-*pent*-2-*en*-4-*ynyl*)*mercury* (13·5 g., 94%) as plates, m. p. 48°, unaltered after several further recrystallisations from pentane (Found: Hg, 61·0. $C_{10}H_{10}Hg$ requires Hg, 60·6%). Light absorption: Max. 2035 and 2480 Å; ε = 25,000 and 27,000.

*Di*-(trans-*pent*-2-*en*-4-*ynyl*)*mercury*. *trans*-Pent-2-en-4-yne (2·0 g.) and the reagent solution (35 c.c.) similarly gave, after recrystallisation from benzene, *di*-(trans-*pent*-2-*en*-4-*ynyl*)*mercury* (4·6 g., 92%) as fine needles, m. p. 141—148° (decomp.) (Found: Hg, 60·5%). Light absorption: Max. 2030 and 2490 Å; ε = 31,000 and 30,000.

cis-*Pent*-2-*en*-4-*yne*. Di-(*cis*-pent-2-en-4-ynyl)mercury (13·0 g.) was heated under reflux with water (50 c.c.) and potassium cyanide (20·0 g.) for 2½ hr. After cooling, the regenerated hydrocarbon was distilled into a trap cooled in carbon dioxide–acetone, and, after drying ($CaCl_2$), redistillation gave *cis*-pent-2-en-4-yne (1·7 g.), b. p. 44·5—45°, $n_D^{22.5}$ 1·4321, the infra-red and ultra-violet spectra of which were virtually the same as those of fraction 6.

*Stability of* cis- *and* trans-*pent*-2-*en*-4-*yne*. The two hydrocarbons, particularly the *cis*-form, were unstable in air even at −5° in the absence of light. The refractive index rose rapidly at first, the liquids becoming yellow. The *cis*-form, distilled after storage in the dark at −5° for 7 days, gave a residue (peroxide?) which detonated violently at 100°; quinol appeared to improve the stability. Measurements of absorption-spectra and $n$ were made on freshly redistilled samples. The *cis*-isomer had $n_D^{20}$ 1·4330, the *trans*-form $n_D^{20}$ 1·4368; the temperature coefficients were 0·00064 and 0·00067 per degree respectively (a range of 15° was investigated and a linear graph obtained in each case).

The authors thank Professor E. R. H. Jones, F.R.S., for his interest and advice. One of them (J. L. H. A.) acknowledges a maintenance grant from the Department of Scientific and Industrial Research.

THE UNIVERSITY, MANCHESTER. [*Received, April 30th*, 1953.]

## 658. *The Properties of Penta-1 : 3-diyne.*

By E. R. H. Jones and M. C. Whiting.

Penta-1 : 3-diyne was first reported by Prévost (*Ann. Chim.*, 1928, **10**, 356), who obtained a hydrocarbon, b. p. 54—56°, by the action of potassium hydroxide on 1 : 2 : 3 : 4-tetrabromopentane. A substance, b. p. 55°, to which this structure was assigned was isolated from the residues obtained in the Hüls acetylene process (see Copenhaver and Bigelow, "Acetylene and Carbon Monoxide Chemistry," New York, 1949, p. 302). The next reference to it was made by Schlubach and Wolf (*Annalen*, 1950, **568**, 141) who found b. p. (*a*) 75—78·5° and (*b*) 76—77° for hydrocarbons obtained by the action of sodium acetylide on (*a*) methylene dichloride and (*b*) propargyl bromide, and considered both to be penta-1 : 3-diyne, formed by prototropic rearrangement of penta-1 : 4-diyne. Independently, Armitage, Jones, and Whiting had already prepared penta-1 : 3-diyne by the action of methyl iodide on monosodiodiacetylene and observed a boiling point of 76·5° (*J.*, 1952, 1993), and later Cook, Jones, and Whiting (*J.*, 1952, 2883) prepared this compound, b. p. 76°, by the action of sodamide on 1 : 4-dichloropent-2-yne. Recently Herbertz (*Ber.*, 1952, **85**, 475) has described "penta-1 : 3-diyne," b. p. 54—56°, obtained by the action of *sodium*, followed by methyl sulphate, on diacetylene, and, without referring to the two syntheses already published by Schlubach and Wolf, quoted Prévost's early work in support of his conclusions.

It is the purpose of the present communication to draw attention to the confused state of the literature on this compound. Our belief that the substance obtained in the laboratories at Manchester and those of Professor Schlubach, b. p. about 76°, is actually penta-1 : 3-diyne depends mainly on the proof from the former (*J.*, 1952, 1998) that its ultra-violet spectrum resembles that of hexa-2 : 4-diyne, and from the latter (*loc. cit.*) that this crystalline hydrocarbon can be obtained from it by methylation; much additional evidence is however cited in the publications referred to and later papers from these schools. On the other hand, neither Prévost nor Herbertz gave any evidence which would exclude the empirical formula $C_5H_6$ for their products. The physical constants tabulated suggest that these were probably mixtures of pent-1-en-3-yne and *trans*-pent-2-en-4-yne, which might not unreasonably be expected from the reactions employed, since (*a*) debromination

*Physical constants of "penta-1 : 3-diyne."*

| | B. p. | $d_4^t$ * | $n_D$ (temp.) |
|---|---|---|---|
| Prévost | 54—56° | 0·7375 (21°) | 1·4431 (21°) |
| Herbertz | 54—56 | 0·7375 (?) | 1·44305 (20°) |
| Schlubach and Wolf (*a*) | 75—78·5 | 0·7926 (20°) | 1·4717 (20°) |
| (*b*) | 76—77 | 0·7909 (20°) | 1·4817 (20°) |
| Armitage *et al.* | 76·5 | — | 1·4790 (15°) |
| Cook *et al.* | 76 | — | 1·4750 (18°) |
| $H_2C{:}CH{\cdot}C{\vdots}C{\cdot}CH_3$ [1] | 59·2°/760 mm. | 0·7401 (20°) | 1·4496 (20°) |
| *trans*-$CH_3{\cdot}CH{:}CH{\cdot}C{\vdots}CH$ [2] | 52·1°/766 mm. | — | 1·4368 (20°) |

* Temp. (*t*) in parentheses.

[1] Jacobson and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 1750. [2] Allan and Whiting, preceding note.

to an olefin, rather than dehydrobromination to an acetylene, has already been observed when a 1 : 2-dibromide was treated with a strong base (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and (*b*) sodium would be expected to *reduce* diacetylene to vinylacetylene, and methylation would then give pent-1-en-3-yne which might perhaps rearrange partly to the more acidic $\Delta^1$-acetylene in the presence of excess of sodamide.

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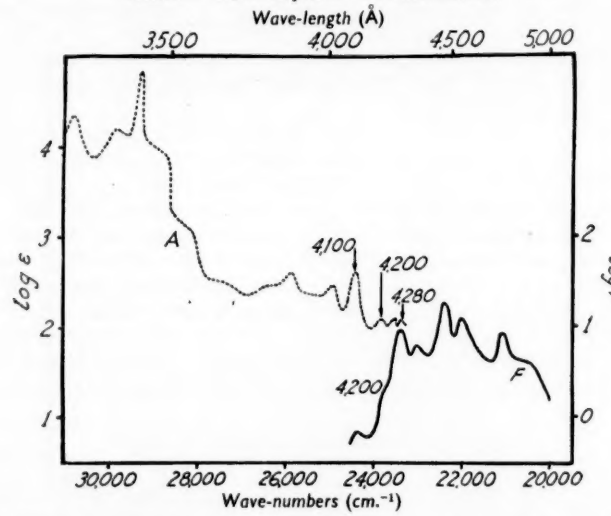
## 659. *The Fluorescence Spectrum of Coronene.*

By B. Brocklehurst.

Coronene has exceptional interest on account of its high degree of symmetry. Its absorption spectrum in benzene solution has been recorded by Clar (Clar, " Aromatische Kohlenwasserstoffe," Springer, Berlin, 1941), but there is no report of its fluorescence spectrum. The absorption spectrum consists of a very strong set of bands below 3600 Å, and a much weaker absorption between 3600 and 4100 Å, with some very weak bands beyond 4100 Å. In order to throw light on the relations between these sets of bands, the fluorescence spectrum of coronene in benzene has been measured.

The apparatus consisted of a Hilger double monochromator with a photo-electron multiplier attached to the exit slit. The response of the multiplier was further amplified to give readings on a micro-ammeter. The solution was placed in a silica cell in front of the monochromator slit, and was illuminated by light of wave-length 3135 Å from a mercury

*Absorption and fluorescence spectra of coronene plotted against wave-numbers, to show the mirror-image relation. A, Absorption. F, Fluorescence.*




lamp equipped with a suitable filter. The instrument was calibrated with a mercury lamp and thermopile, and the results are expressed in relative quanta.

The fluorescence spectrum (Figure, curve F) covers the range 4100—4800 Å, and shows much sharper fine structure than usual for hydrocarbons. The Figure shows that the fluorescence spectrum is the mirror image of the absorption (curve *A*) between 3600 and 4100 Å. This absorption must therefore correspond to a distinct, though but weakly allowed, transition to the lowest excited singlet state.

This conclusion is confirmed by measurements on the quenching of coronene fluorescence in chloroform by dissolved oxygen. Measurements were made at a fixed wave-length, the solution being saturated first with air then with purified coal-gas. The quenching constant (in the Stern–Volmer equation) is 4800 approximately. The " reaction rate " between coronene and oxygen is then given by 4800/(fluorescence efficiency) × (life-time of excited state). The fluorescence efficiency was calculated by measuring the area under the fluorescence spectrum and comparing it with that of anthracene. Taking the efficiency of anthracene as 0·24 (Bowen and Williams, *Trans. Faraday Soc.*, 1939, **35**, 765), and correcting for oxygen and concentration quenching, give a value 0·3 for coronene. The life-time of the excited state was calculated from the area of the absorption spectrum between 3600 and 4300 Å, by the equation of Lewis and Kasha (*J. Amer. Chem. Soc.*, 1945,

67, 994), and the value of about $2 \times 10^{-7}$ sec. was obtained. This gives $8 \times 10^{10}$ l.-mol.$^{-1}$ sec.$^{-1}$ for the " reaction rate " which may be compared with $6 \times 10^{10}$ for anthracene (Bowen and Cook, unpublished work). If the coronene absorption band below 3600 Å represented the transition involved, this rate would be 100 times greater.

The weak absorption bands at 4280 and 4200 Å (23,360 and 23,800 cm.$^{-1}$) and the fluorescence bands at 4200 and 4100 Å (23,800 and 24,400 cm.$^{-1}$) are unusual and lead to the suggestion that transitions between the ground state and the lowest excited state are forbidden by symmetry, but become allowed when coupled with changes in the vibrational energy. This is to be expected from the analogy with benzene which has the same high degree of symmetry.

The first strong bands in the two spectra are, therefore, 0—1 transitions (4100 Å in absorption, 4280 Å in fluorescence) while the absorption at 4280 Å and the fluorescence at 4100 Å represent 1—0 transitions and should therefore be temperature-dependent. If this assignment is not correct, the gap between the main parts of the spectra could be explained by solvent interaction, but the presence of the weak bands would offer difficulty. In both spectra there is a weak band at 4200 Å, presumably corresponding to a 0—0 transition, *i.e.*, the transition is not completely forbidden in the absence of vibrational coupling.

Clar also reports an absorption band at 4260 Å, but no corresponding band occurs in chloroform solution (Patterson, *J. Amer. Chem. Soc.*, 1942, **64**, 1485), so that the observation may be incorrect. It is difficult to check this because of the low solubility of coronene in benzene.

I thank Dr. E. J. Bowen, F.R.S., under whose supervision this work was carried out, and Professor Wilson Baker, F.R.S., who provided a sample of pure coronene.

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## 660. *Dambonitol: Its Isolation from* Dyera lowii *and* Dyera costulata *and Its Constitution.*

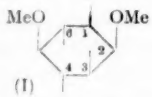
By A. J. COMOLLO and A. K. KIANG.

THE Dyera tree (or " jelutong "), indigenous to western Malasia, belongs to the family Apocyanaceae. It is of some economic importance as its latex is a source of the plastic " gum " (gutta jelutong), which is used in the manufacture of chewing gum. The latex is coagulated by the addition of phosphoric acid which gives a product with enhanced storage qualities (Georgi, *Malayan Forester*, 1934, **3**, 181; 1935, **4**, 8), and the serum, after the gutta is separated off, is run to waste.

From the serum of the latex of the Borneo tree, *Dyera lowii*, and of the Malayan tree, *D. costulata*, we obtained dambonitol which has previously been isolated from the latex of Gabbon rubber (Girard, *Compt. rend.*, 1868, **67**, 820), the juice of *Castilloa elastica* (Weber, *Ber.*, 1903, **36**, 3108), and Sumatran rubber latex (De Jong, *Rec. Trav. chim.*, 1908, **27**, 257). The serum from each source forms approximately 70% of the latex and contains 2—2·5% of dambonitol. Dambonitol gives a weak Scherer's reaction, does not reduce Fehling's solution, and forms a tetra-acetate. It contains two methoxy-groups, and both it and its tetra-acetate, when evaporated with excess of hydriodic acid, give *meso*inositol.

As far as we are aware, the constitution of dambonitol has not previously been established. Dambonitol is optically inactive, so the methoxy-groups must be in the 1 : 3-, 2 : 5-, or 4 : 6-positions. It does not form a cyclic acetal with acetone under the conditions employed by Posternak (*Helv. Chim. Acta*, 1950, **33**, 350) and Angyal and Macdonald (*J.*, 1952, 686). Although the latter authors have shown that *trans*-hydroxyl groups can lead to an *iso*propylidene derivative in special cases (*e.g.*, *epi*inositol), failure of the reaction in this case proves the absence of *cis*-α-hydroxyl groups; dambonitol is therefore not $O^4O^6$-dimethylinositol.

It is well known that, on oxidation with sodium metaperiodate, *meso*inositol (Fleury, Poiret, and Fivet, *Compt. rend.*, 1945, **220**, 664; Stephen, *J.*, 1952, 738) and its monomethyl ether, sequoyitol (Riggs, *J.*, 1949, 3199), consume much more than the amounts required for glycol fission and give rise to comparatively large amounts of strong acids. In contrast with these results, we have found that, dependent on the concentration of the periodate, the oxidation of dambonitol is practically ended in 4—5 hours with the consumption of two mols. of periodate. The resulting solution strongly reduces ammoniacal silver nitrate and Fehling's solution; a small but finite amount of "strong acid" is produced. Thus dambonitol is the 2 : 5-dimethyl ether of *meso*inositol, as the 1 : 3-isomer would certainly




(I)

$$OCH{\cdot}CH(OMe){\cdot}CHO \rightleftharpoons CHO{\cdot}C(OMe){:}CH{\cdot}OH$$

(II)

have produced at least one equivalent of formic acid per two mols. of periodate consumed. It is probable that in the oxidation dambonitol gives rise to two mols. of *O*-methyltartronaldehyde (II). The production of the "strong acid" up to a limiting amount of only 0·2—0·3 equivalent, on rapid consumption of up to 2 mols. of periodate, suggests that the acid is not produced by oxidation of the dialdehyde: the acidity may be due to the enol form of the dialdehyde. *O*-Methyltartronaldehyde may be less easily oxidised than tartronaldehyde by sodium metaperiodate, and it is worthy of note that malondialdehyde is less stable than its α-bromo- or its α-nitro-derivative (Hüttel, *Ber.*, 1941, **74**, 1825).

*Experimental.—Isolation of dambonitol.* The serum containing phosphoric acid was neutralised with ammonia and concentrated on a steam-bath to one-fifth of its volume. The light brown solution was filtered from the proteinaceous precipitate and treated with a hot solution of strontium hydroxide until no more precipitate was formed. The filtered solution was evaporated to dryness on a steam-bath. The slightly coloured residue was finely powdered and extracted (Soxhlet) with ethanol (6 c.c. per g.) until only a small amount of brown material remained. The crystals which appeared from the cooled extract were filtered off and, after being washed with ethanol, were practically colourless and had m. p. 200—208°. The mother-liquor and washings were evaporated to dryness and the residue heated with acetic anhydride (4 c.c./g.) and pyridine (0·5 c.c./g.) for 1—1½ hr. In this way dambonitol tetra-acetate was obtained. On the average, 1 l. of serum gave 20 g. of dambonitol and 12 g. of its tetra-acetate.

Two crystallisations of dambonitol from 95% ethanol (12 c.c./g.) gave colourless slender prisms, m. p. 210° (lit., m. p. 190°, 195·5°, and 206°) (Found: C, 46·1; H, 7·9; OMe, 30·4, 29·35. Calc. for $C_8H_{16}O_6$: C, 46·15; H, 7·75; OMe, 29·8%). The compound had a sweet taste, and was hygroscopic.

| Time (hr.): | ½ | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Periodate uptake.* | | | | | |
| Solution a ..... | 1·10 | 1·43 | 1·79 | 1·91 | 1·98 | 2·02 | 2·00 | 2·01 | 2·08 |
| ,, b ..... | 1·36 | 1·86 | 1·93 | 1·97 | 1·98 | 2·00 | 2·02 | 2·00 | 2·00 |
| ,, c ..... | 1·76 | 1·98 | 2·12 | 2·16 | 2·14 | 2·18 | 2·20 | 2·20 | 2·20 |
| ,, d ..... | 1·77 | 2·00 | 2·12 | 2·14 | — | — | — | — | 2·14 |
| | | | | *Strong acid liberated.* | | | | | |
| Solution b ..... | — | — | 0·18 | 0·21 | 0·21 | 0·22 | 0·22 | 0·23 | 0·24 |
| ,, c ..... | — | 0·19 | 0·22 | 0·22 | 0·24 | 0·22 | 0·22 | 0·24 | 0·26 |
| ,, d ..... | 0·11 | 0·15 | — | 0·17 | — | — | 0·17 | — | 0·20 |

Solution a: $x = 0{\cdot}05967$; $y = 0{\cdot}2865$; $z = 0{\cdot}2470$.
,, b: $x = 0{\cdot}07600$; $y = 0{\cdot}365$; $z = 0{\cdot}4855$.
,, c: $x = 0{\cdot}07001$; $y = 0{\cdot}3363$; $z = 0{\cdot}665$.
,, d: dambonitol (0·07496 g., 0·36 millimole) was dissolved in 0·2495M-sodium metaperiodate (100 c.c.).

*Dambonitol tetra-acetate.* Dambonitol (0·5 g.) was heated under reflux with acetic anhydride (2·5 c.c.) for 1 hr. The product was poured into excess of water. The precipitate, recrystallised from methanol, had m. p. 195° (Maquenne, *Compt. rend.*, 1887, **104**, 1853, and De Jong, *loc. cit.*, give m. p. 193° and 195° respectively) (Found: C, 50·9; 51·1; H, 6·5, 6·65. Calc. for $C_{16}H_{24}O_{10}$: C, 51·1; H, 6·4%).

*Demethylation.* Dambonitol (0·5 g.) was evporated to dryness with constant-boiling hydriodic acid (2 c.c.) on a steam-bath. Water (2 c.c.) was added and the mixture again evaporated to dryness. The residue was rubbed, and the resulting crystals washed with ethanol (yield, 0·25 g.; m. p. 218—224°). Recrystallised by dissolution in the minimum amount of hot water and careful addition of ethanol, the product melted at 224—225°, undepressed by *meso*inositol.

Dambonitol tetra-acetate, treated in the same way, also gave *meso*inositol.

*Periodate oxidation.* Dambonitol (*x* g., *y* millimole) was dissolved in *z*M-metaperiodate (50 c.c.) and the solution made up to 100 c.c. with water. The mixture was kept in the dark at 27—28°. At intervals portions (5 c.c.) were treated with M-sodium hydrogen carbonate (2 c.c.), potassium iodide (0·1 g.), and 0·025N-sodium arsenite solution (15 c.c.), and after 5 min. the excess of arsenite was titrated against 0·025N-iodine. Further portions (5 c.c.) were rapidly titrated against 0·01N-sodium hydroxide (methyl-red). Consumption of periodate (moles/mole) and " strong acid " liberated (equiv./mole) are shown in the Table.

The authors thank Messrs. Malayan Guttas Ltd., and Lee Sawmills Ltd., Singapore, for the supply of the latex of *D. lowii* and *D. costulata* respectively, and Professor R. A. Robinson for his interest.

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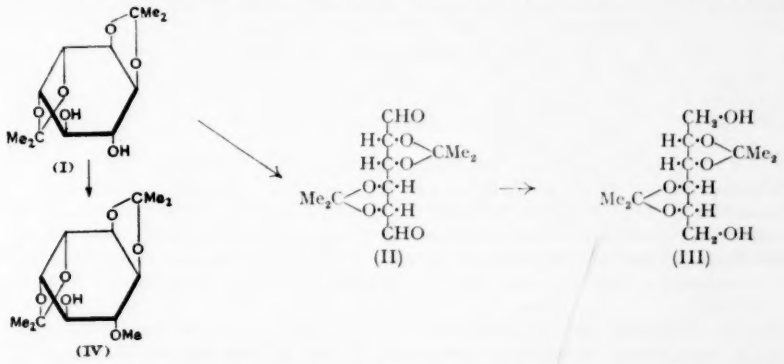
## 661. *The Structure of the Di-*O*-isopropylidene Derivatives of (−)-Inositol and Pinitol.*

By S. J. ANGYAL, C. G. MACDONALD, and N. K. MATHESON.

THE structures of the compounds named in the title were established as **1 : 2-5 : 6**-di-*O-iso*propylidene-(−)-inositol (I) and 3-*O*-methyl-**1 : 2-5 : 6**-di-*O-iso*propylidene-(+)-inositol, respectively, on the assumption that acetal formation occurred between hydroxyl groups in *cis*-positions only (Angyal and Macdonald, *J.*, 1952, 686). While this assumption is, by past experience, reasonable, the recent discovery of derivatives in which *trans*-hydroxyl groups had combined with acetone (*idem, loc. cit.*) made an independent determination of these structures desirable. Anderson, Fischer, and MacDonald (*J. Amer. Chem. Soc.*, 1952, **74**, 1479) degraded di-*O-iso*propylidenepinitol to di-*O*-methyl-(−)-tartaric acid but this, again, needs the assumption of *cis*-acetal formation in order to serve as a proof of structure.

The correctness of structure (I) has now been proved by the following reactions: (I) was oxidised by lead tetra-acetate to a dialdehyde (II) which by the Meerwein–Ponndorf




reaction yielded a **2 : 3-4 : 5**-di-*O-iso*propylidenehexitol (III), shown to be a derivative of L-mannitol by hydrolysis to the latter. Isolation of L-mannitol indicates that positions 1, 2, 5, and 6 of (−)-inositol are involved in acetal formation and thereby proves the **1 : 2-5 : 6**-di-*O-iso*propylidene structure since the alternative **1 : 6-2 : 5**- and **1 : 5-2 : 6**-structures are sterically impossible.

These reactions, incidentally, confirm the configuration of (−)-inositol established by Posternak (*Helv. Chim. Acta*, 1936, **19**, 1007).

After this work had been completed, Ballou and Fischer reported (Amer. Chem. Soc. Meeting, Los Angeles, March, 1953) a similar degradation with (+)-inositol (*J. Amer. Chem. Soc.*, in the press). Their data agree well with ours.

1 : 2-3 : 4-Di-*O-iso*propylidene*epi*inositol was similarly oxidised to a dialdehyde which has not yet been further investigated.

The structure of 1 : 2-5 : 6-di-*O-iso*propylidenepinitol was confirmed by preparation of its enantiomorph (IV) from (I) by methylation. This proves that the acetal rings have the same position in the two compounds.

*Experimental.*—L-manno-2 : 3-4 : 5-*Di*(iso*propylidenedioxy*)*adipic dialdehyde* (II). To a solution of di-*O-iso*propylidene-(−)-inositol (4·07 g., 1 mol.) in dry chloroform (80 ml.) lead tetra-acetate (6·93 g., 1 mol.) was added and the mixture was vigorously shaken for 15 min. The separated lead acetate was filtered off and washed with chloroform, and the filtrate was evaporated under reduced pressure. The semicrystalline residue was extracted with boiling light petroleum (b. p. 60—90°; 100 ml.) which left some lead acetate undissolved; on cooling, the solution deposited crystals of the *dialdehyde* (3·29 g., 82%), m. p. 133—134°, $[\alpha]_D^{18}$ +12° (*c*, 2·5 in abs. EtOH) (Found: C, 55·9; H, 7·25. $C_{12}H_{18}O_6$ requires C, 55·8; H, 7·05%).

When a solution of *p*-nitrophenylhydrazine in acetic acid was added to an aqueous solution of the dialdehyde, the *bis*-p-*nitrophenylhydrazone* was precipitated. After several crystallisations from acetone–light petroleum it formed pale yellow blades, m. p. >250°, strongly dependent on the rate of heating (Found: N, 16·3. $C_{24}H_{28}O_8N_6$ requires N, 15·9%).

The dialdehyde was not reduced by hydrogen and palladised charcoal or Adams's catalyst, or by sodium amalgam in dilute acetic acid.

2 : 3-4 : 5-*Di*-O-iso*propylidene*-L-*mannitol* (III). After being shaken for 20 min., a mixture of di-*O-iso*propylidene-(−)-inositol (1·82 g.), lead tetra-acetate (3·10 g.), and dry chloroform (30 ml.) was filtered and evaporated under reduced pressure at 35°. A solution of aluminium *iso*propoxide (2·9 g.) in *iso*propanol (50 ml.) was added and the milky suspension slowly distilled until a test for acetone in the distillate was negative. The volume was kept constant by occasional additions of *iso*propanol. The solvent was removed under reduced pressure at 45°, and ice-cold sodium hydroxide solution (14 ml., 20%) was added. An oil separated which was extracted by ether (3 × 14 ml.); the ether was dried and evaporated, and the residual viscous oil dissolved in chloroform and washed with water. The chloroform was boiled off and the residue crystallised from benzene, to give a crop (0·28 g.), m. p. 87—89°; a second crop (0·17 g.) was obtained by the addition of light petroleum to the mother-liquor. Recrystallisation from light petroleum and sublimation at 120°/1 mm. gave pure *di*-O-iso*propylidene*-L-*mannitol*, m. p. 91·5°, $[\alpha]_D^{26}$ +1° (*c*, 1·1 in abs. EtOH) (Found: C, 54·5; H, 8·5. $C_{12}H_{22}O_6$ requires C, 54·95; H, 8·45%).

Hydrolysis of this compound with 0·1N-hydrochloric acid on the steam-bath for 10 min. gave a quantitative yield of L-mannitol, m. p. 165—166° (corr.) (Found: C, 39·75; H, 7·75. Calc. for $C_6H_{14}O_6$: C, 39·55; H, 7·75%) {hexabenzoate, m. p. 151—152° (corr.), $[\alpha]_D^{21}$ −50° (*c*, 1·8 in $CHCl_3$)} (Found: C, 71·35; H, 4·6. Calc. for $C_{48}H_{38}O_{12}$: C, 71·45; H, 4·75%). For L-mannitol Baer and Fischer (*J. Amer. Chem. Soc.*, 1939, **61**, 761) reported m. p. 163—164° (uncorr.); for the hexabenzoate of D-mannitol Power and Rogerson (*J.*, 1910, **97**, 1944) reported m. p. 149° (uncorr.), $[\alpha]_D$ +50·7° (*c*, 2·1 in $CHCl_3$).

allo-2 : 3-4 : 5-*Di*(iso*propylidenedioxy*)*adipic dialdehyde*. To a solution of 1 : 2-3 : 4-di-*O-iso*propylidene*epi*inositol (0·130 g.) (Angyal and Macdonald, *loc. cit.*) in dry chloroform (5 ml.) lead tetra-acetate (0·222 g.) was added and the mixture was vigorously shaken for 15 min. The separated lead acetate was filtered off and the filtrate evaporated under reduced pressure. The residue was extracted with light petroleum (3 × 4 ml.), which was evaporated; the residual solid, twice sublimed at 100°/0·5 mm., gave the *dialdehyde* (0·06 g., 45%), m. p. 102° (Found: C, 55·5; H, 7·2%).

3-O-*Methyl*-1 : 2-5 : 6-*di*-O-iso*propylidene*-(−)-*inositol* (IV). Di-*O-iso*propylidene-(−)-inositol (0·5 g.) was heated under reflux with methyl iodide (12 ml.) and silver oxide (0·6 g.) for 25 hr. The solution was filtered and the precipitate washed with acetone. The solvent was evaporated and the residue sublimed at 105—115° (bath-temp.)/1 mm. The sublimate, recrystallised several times from light petroleum, yielded the inositol derivative (0·1 g., 19%), m. p. 102—104°, $[\alpha]_D^{16}$ +45° (*c*, 1·3 in $CHCl_3$). For di-*O-iso*propylidenepinitol Anderson *et al.* (*loc. cit.*) reported m. p. 104·5—106°, $[\alpha]_D^{23}$ −45·4°.

When methylation was continued for 60 hr., an 85% yield of 3 : 4-*di*-O-*methyl*-1 : 2-5 : 6-*di*-O-iso*propylidene*-(−)-*inositol*, m. p. 88—89°, was obtained (Found : C, 58·6; H, 8·3. $C_{14}H_{24}O_6$ requires C, 58·3; H, 8·4%). For the enantiomorph Anderson *et al.* found m. p. 88—90°.

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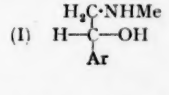
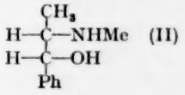
## 662. *The Configuration of Noradrenaline and Adrenaline.*

By C. E. DALGLIESH.

THE configuration of natural (−)-adrenaline and (−)-noradrenaline appears never to have been determined. Freudenberg (" Stereochemie," Deuticke, Leipzig, 1932, p. 697) assigned to (−)-adrenaline the configuration (I) [here and elsewhere, Ar = 3 : 4-$(HO)_2C_6H_3$]. No chemical evidence was produced to support this conclusion, which was based on the lævorotation of both (−)-adrenaline and (−)-ephedrine (II). The configuration of (−)-ephedrine is unambiguous (cf. Leithe, *Ber.*, 1932, **65**, 660; Freudenberg, Schoeffel, and Braun, *J. Amer. Chem. Soc.*, 1932, **54**, 234; Freudenberg and Nikolai, *Annalen*, 1934, **510**, 223) but rotational analogy for assignment of configuration is well known from Freudenberg's own work to be of uncertain reliability. Evidence now exists in the literature clearly establishing the configuration of adrenaline, which is in fact the opposite of that proposed by Freudenberg. The difference between the configurations at the β-carbon atoms of (−)-adrenaline and (−)-ephedrine raises interesting pharmacological questions.



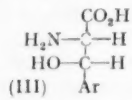



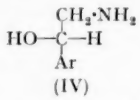

Dalgliesh and Mann (*J.*, 1947, 658) prepared β-3 : 4-dihydroxyphenylserine, by condensation of glycine ester and an aromatic aldehyde, and obtained only one of the two possible racemates. The stereochemistry of the product was not determined, but on enzymic decarboxylation one optical isomer of the racemate was decarboxylated to give (−)-noradrenaline (Blaschko, Holton, and Sloane-Stanley, *Brit. J. Pharmacol.*, 1948, **3**, 315; Blaschko, Burn, and Langemann, *ibid.*, 1950, **5**, 431). Dalgliesh later (*J.*, 1949, 90) prepared β-*p*-nitrophenylserine by the same method, and here again only one of the possible racemates was obtained. Interest in β-*p*-nitrophenylserine was stimulated by its relation to chloromycetin and many workers examined its stereochemistry. This work clearly showed that the method used by Dalgliesh for preparation of β-*p*-nitrophenylserine gave the *erythro*-racemate (Holland, Jenkins, and Nayler, *J.*, 1953, 273, and collected references therein). In particular β-*p*-hydroxyphenylserine prepared by this route also has the *erythro*-configuration (Holland *et al.*, *loc. cit.*). It is thus reasonable to assume that it is one optical isomer of the *erythro*-β-3 : 4-dihydroxyphenylserine which is decarboxylated to (−)-noradrenaline. Further confirmation has been provided by Fodor and Kiss (*Acta Univ. Szeged, Chem. et Phys.*, 1950, **3**, 26) who prepared β-3 : 4-dihydroxyphenylserine by a quite different route (involving nitrosation of an ω-carboxyacetophenone derivative), and obtained only one racemate which they found to be *erythro*, and which was enzymically decarboxylated to (−)-noradrenaline. Other β-phenylserine derivatives prepared by this second route also have the *erythro*-configuration (Hartung, Dittrich, and Chang, *J. Amer. chem. Soc.*, 1953, **75**, 238).

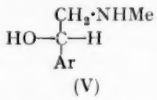
The decarboxylases which convert *erythro*-β-3 : 4-dihydroxyphenylserine into (−)-noradrenaline are specific for L-amino-acids (see Blaschko, *J. Physiol.*, 1942, **101**, 337; Blaschko, Holton, and Sloane-Stanley, *ibid.*, 1949, **108**, 427; and review by Schales, Chap. 50, in " The Enzymes," ed. Sumner and Myrbäck, Academic Press, New York, 1951, Vol. II, Part I, p. 216). The isomer undergoing decarboxylation must therefore be (III), and (−)-noradrenaline must therefore be (IV). This is confirmed by the work of Fones (*Arch. Biochem. Biophys.*, 1952, **36**, 486) who, using snake venom preparations, showed that

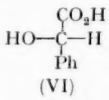
enzymic deamination and oxidation of *threo*-β-phenyl-DL-serine gave D(−)-mandelic acid, and of *erythro*-phenyl-DL-serine gave L(+)-mandelic acid. As again only the L-isomers of amino-acids are deaminated by such preparations the isomer of β-phenylserine analogous to (III) gave L(+)-mandelic acid (VI). It should be mentioned that enzymic attack at the α-carbon atom does not cause inversion at the β-carbon atom (Meister, *Nature*, 1951, **168**, 1119). Moreover *threo*-β-phenyl-$D_s$-serine has been correlated chemically with L-mandelic acid, and *threo*-β-phenyl-$L_s$-serine with phenyl-L-alanine (Vogler, *Helv. Chim. Acta*, 1950, **33**, 2111) in agreement with the above configurational assignments.

It is only recently that the physiological importance of (−)-noradrenaline has been realised and its properties determined (Tainter, Tullar, and Luduena, *Science*, 1948, **107**, 39; Tullar, *J. Amer. Chem. Soc.*, 1948, **70**, 2067), and the configurations of (−)-noradrenaline


(III)


(IV)


(V)


(VI)

and (−)-adrenaline have never been chemically correlated. However, there is much indirect evidence that these configurations are identical. Their structures are so similar that the analogous lævorotation itself carries much more weight than Freudenberg's analogy of adenaline with ephedrine (which contains an additional asymmetric carbon atom). Natural adrenaline and noradrenaline very frequently occur together (cf., *e.g.*, Goldenberg *et al.*, *Science*, 1949, **109**, 534; Tullar, *ibid.*, p. 536) and both are in all probability derived from β-phenylalanine (cf., *e.g.*, Gurin and Delluva, *J. Biol. Chem.*, 1947, **170**, 545) or the biogenetically equivalent tyrosine, *via* a common precursor. Noradrenaline is readily converted into adrenaline by suprarenal tissue both *in vitro* and *in vivo* (Bülbring, *Brit. J. Pharmacol.*, 1949, **4**, 234; Bülbring and Burn, *ibid.*, p. 245), the *N*-methyl groups in adrenaline being derived by transmethylation from methionine (Keller, Boissonnas, and du Vigneaud, *J. Biol. Chem.*, 1950, **183**, 627). There is no reason to suspect inversion of the CH·OH group in these reactions, and it is unlikely that a change from a $CH_2{\cdot}NH_2$ group to a $CH_2{\cdot}NHMe$ group would cause a reversal of the sign of rotation. There is therefore a very high degree of probability that (−)-adrenaline has the configuration (V).

There is no universally accepted rule for representing the correlation of configuration of a substance such as adrenaline with that of glyceraldehyde. If it were accepted that correlation should be as indicated by the projection formulæ (IV) and (V), then (−)-noradrenaline and (−)-adrenaline would become L-noradrenaline and L-adrenaline. As the prefix L is often (unjustifiably) used for these substances (*e.g.*, by Goldenberg *et al.* and by Tullar, *locc. cit.*), orientation as in (IV) and (V) would have the dual advantages of avoiding confusion and of making the naturally occurring isomer L, as for the amino-acids.*

I thank Dr. H. Blaschko, Dr. A. Neuberger, F.R.S., and Dr. W. Klyne for valuable discussions.

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* The assignment of L to (IV) and (V) proposed by the author is the opposite to that which follows from the Cahn–Ingold sequence rule (*J.*, 1951, 612). It is the same as that which follows from the proposals by Klyne (*Chem. and Ind.*, 1951, 1022) and others provided that noradrenaline (IV) is considered to be systematically named as 3 : 4 : β-trihydroxyphenethylamine, but the same proposals lead to the opposite (D) assignment for this stereoisomer on the basis of 2-amino-1-(3 : 4-trihydroxyphenyl)-ethanol. In such cases it may well be preferable, owing to lack of agreement, to use the italic capital letter together with such special conventions as an author wishes [in this case, *L* for (IV) and (V)], as was done by Linstead and his collaborators for a series of acids (*J.*, 1951, 1131 and later papers). However, the Editor, having been concerned in the published arguments, considers it inappropriate to do more than point out the present position. ED.

## 663. *The Degradation of Digoxigenin.*

By D. A. H. Taylor.

Steiger and Reichstein (*Helv. Chim. Acta*, 1938, **21**, 828) degraded digoxigenin diacetate by permanganate oxidation, etc., eventually obtaining a dihydroxy-acid and the corresponding diketo-acid, which was identified as 3 : 12-diketoetianic acid (Mason and Hoehn, *J. Amer. Chem. Soc.*, 1938, **60**, 2824), thus providing convincing evidence for the formulation of digoxigenin as a 3 : 12 : 14-trihydroxycard-20 : 22-enolide. The dihydroxy-acid was shortly afterwards identified with 3α : 12β-dihydroxyetianic acid (*idem, ibid.*, 1939, **61**, 1614); however the details of the comparison were perhaps not entirely satisfactory as derivatives were not prepared; and as all other cardiac aglycones and steroidal sapogenins whose constitution has since been proved have the 3β-configuration, it appeared of interest to repeat the degradation of digoxigenin. When this had been done, the author was informed by Professor T. Reichstein and by Dr. H. M. E. Cardwell that they had each independently shown that digoxigenin had the 3β-configuration. The present paper therefore reports only the details of the degradation which had already been carried out.

*Experimental.*—Rotations were measured in a 4-dm. tube, and m. p.s on the Kofler block.

3β : 12β-*Diacetoxy*-14β-*hydroxyetianic acid.* Digoxigenin diacetate (2·0 g.), in ethyl acetate (200 c.c.), was ozonised at −80°. When the solution had become deep blue it was allowed to warm to 0° and treated with zinc powder (2 g.) and acetic acid (10 c.c.). After being kept for 1 hr. the solution was washed with water, dried, and evaporated. The residue was taken up in methanol (130 c.c.), treated with potassium hydrogen carbonate (2 g.) in water (60 c.c.), and set aside overnight. The solution was then diluted with water and ethyl acetate and the organic layer evaporated, the residue being oxidised overnight with periodic acid (1·8 g.) in water (10 c.c.) and dioxan (100 c.c.). The acidic fraction of the product, crystallised from methanol, yielded the etianic acid (1·26 g.), m. p. 231—234°, $[\alpha]_D^{20}$ +38·4° ± 2° (*c*, 0·3 in $CHCl_3$). Steiger and Reichstein give m. p. 229—230°. The *methyl* ester, prepared with diazomethane, crystallised from methanol in plates, m. p. 183—184°, $[\alpha]_D^{21}$ +55·5° ± 0·5°, $[\alpha]_{5461}^{21}$ +64·3° ± 0·5° (*c*, 1 in $CHCl_3$) (Found: C, 66·4; H, 8·35. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%).

*Methyl* 3β : 12β-*diacetoxyeti*-14-*enate.* Methyl 3β : 12β-diacetoxy-14β-hydroxyetianate (1·0 g.) in pyridine (12 c.c.) was treated with freshly distilled phosphorus oxychloride (3 c.c.) and one drop of water. Next morning the mixture was poured on ice and ether, and the organic layer washed with dilute hydrochloric acid, sodium carbonate, and water, dried, and evaporated. The residue, which crystallised, had m. p. at 130—140°, and was chromatographed in benzene on alumina (30 g.). Benzene eluted *methyl* 3β : 12β-*diacetoxyeti*-14-*enate* (770 mg.), crystallising from methanol in fine matted needles, m. p. 144—145°, $[\alpha]_D^{22}$ +66·0° ± 2°, $[\alpha]_{5461}^{22}$ +77° ± 2° (*c*, 0·3 in $CHCl_3$) (Found: C, 69·2; H, 8·5. $C_{25}H_{36}O_6$ requires C, 69·35; H, 8·3%).

*Methyl* 3β : 12β-*diacetoxyetianate.* The foregoing ester (750 mg.) in acetic acid (25 c.c.) was hydrogenated over Adams's catalyst (50 mg.) (uptake complete in 15 min.), filtered from catalyst, and evaporated. The residue gave crystals, m. p. 130—164° (630 mg.), from methanol. Fractional crystallisation from methanol gave *methyl* 3β : 12β-*diacetoxyetianate* (500 mg.) as prisms, m. p. 143—144°, $[\alpha]_D^{22}$ +50·2° ± 2°, $[\alpha]_{5461}^{22}$ +62·8° ± 2° (*c*, 0·6 in $CHCl_3$) (Found: C, 68·8, 69·2; H, 8·6, 8·7. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%). This substance gave no depression of m. p. mixed with a specimen provided by Professor Reichstein which has recently been synthesised in his laboratory (personal communication). From the mother-liquors there was obtained after chromatography on alumina a substance which was probably *methyl* 3β : 12β-*diacetoxy*-14β-*etianate* (45 mg.), crystallising from methanol in pointed prisms, m. p. 206—208°, $[\alpha]_D^{21}$ +63·5° ± 4°, $[\alpha]_{5461}^{21}$ +80·0° ±4° (*c*, 0·2 in $CHCl_3$) (Found: C, 68·9; H, 8·9. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

*Methyl* 3β : 12β-*dihydroxyetianate.* 3β : 12β-Diacetoxyetianic acid was prepared by hydrolysis of the diacetate methyl ester with hot aqueous methanolic potassium hydroxide and crystallised from methanol in needles, m. p. 286—288°, $[\alpha]_D^{23}$ +30·2° ± 1°, $[\alpha]_{5461}^{23}$ +38·6° ± 1° (*c*, 0·6 in MeOH). Steiger and Reichstein give m. p. 282—286° (Found: C, 70·1; H, 9·9. Calc. for $C_{20}H_{32}O_4.\frac{1}{2}CH_3{\cdot}OH$: C, 69·9; H, 9·7%). The methyl ester, prepared with diazomethane, crystallised from methanol in laths, m. p. 187—188° (sublimes in needles above 160° on the Kofler block), $[\alpha]_D^{22}$ +38·2° ± 2°, $[\alpha]_{5461}^{22}$ +45·2° ± 2° (*c*, 0·4 in MeOH) (Found: C, 69·3; H,

10·1. Calc. for $C_{21}H_{34}O_4,CH_3{\cdot}OH$: C, 69·1; H, 9·95%). Steiger and Reichstein give m. p. 180—183°.

The author is grateful to Professor A. Stoll for a generous gift of digoxigenin, and to Dr. R. K. Callow for his interest.

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## 664. *Fluorine-substituted Phenylhydrazines.*

By H. SUSCHITZKY.

THE preparation of fluorophenylhydrazines was of interest in connection with the synthesis of *N*-heteroaromatic fluorine compounds (unpublished work). Reduction of the corresponding fluorobenzenediazonium chlorides with sodium hydrogen sulphite which has been found unsatisfactory for the preparation of halogenophenylhydrazines (Barclay and Campbell, *J.*, 1945, 530) proved unsuccessful also in this case. Stannous chloride in excess of hydrochloric acid was eventually used as a reducing agent under the conditions described by Bülow (*Ber.*, 1918, **51**, 404).

*Experimental.*—Nitrogen determinations were carried out by Kjeldahl's method, those of diazonium-nitrogen by Schiemann and Pillarsky's method (*Ber.*, 1929, **62**, 3035). Diazonium borofluorides were decomposed in a current of dry nitrogen.

o-*Fluorophenylhydrazine.* A fine suspension of *o*-fluoroaniline hydrochloride (from 12·6 g. of *o*-fluoroaniline) in concentrated hydrochloric acid (140 c.c.) was diazotised at −10° with 40% sodium nitrite solution and reduced with stannous chloride (76·8 g.). The resulting creamy precipitate was collected after 1 hr. Excess of acid was removed by washing with cold saturated sodium chloride solution and the pink solid was then transferred to a separator half immersed in a freezing mixture. Addition of a saturated solution of ammonium or sodium acetate (30—50 c.c.) liberated the base which was extracted with ether (2 × 30 c.c.). After drying ($K_2CO_3$) of the extract in the dark, the solvent was evaporated off and the residual oil twice distilled under reduced pressure. o-*Fluorophenylhydrazine* separated as nearly colourless needles from light petroleum (b. p. 60—80°)–ethanol (10 : 1 by vol.) and as plates from benzene; it had m. p. 47°, b. p. 95—96°/9 mm. (7·8 g., 55%), and was unstable to light and air (Found: N, 21·9. $C_6H_7N_2F$ requires N, 22·2%). It gave a *hydrochloride* (precipitated in ether), needles, m. p. 186° (decomp.) (Found: N, 16·8; Cl, 21·4. $C_6H_8N_2ClF$ requires N, 17·2; Cl, 21·8%), glucosazone, m. p. 199° (decomp.), *benzylidene*, m. p. 99° (Found: N, 12·8. $C_{13}H_{11}N_2F$ requires N, 13·0), *salicylidene*, m. p. 126° (Found: N, 12·0. $C_{13}H_{11}ON_2F$ requires N, 12·2), and α-*methylbenzylidene* derivative, m. p. 74° (Found: N, 12·0. $C_{14}H_{13}N_2F$ requires N, 12·3%).

A mixture of *o*-fluorophenylhydrazine (1 mol.) and *cyclo*hexanone (1 mol.) became warm and cloudy. A small quantity of ethanol was added and the mixture heated on a steam-bath (15 min.), then cooled, and ethanol and water were removed under diminished pressure. The residue solidified on trituration with light petroleum (b. p. 60—80°). cyclo*Hexanone* o-*fluorophenylhydrazone* was obtained from light petroleum (b. p. 60—80°)–ether (3 : 1 by vol.) as nearly colourless flakes, m. p. 38° (80%), which decomposed to a brown liquid within 1 hr. (Found: N, 13·2. $C_{12}H_{15}N_2F$ requires N, 13·6%).

m-*Fluorophenylhydrazine*, similarly prepared, crystallised from 1 : 1 ether–light petroleum (b. p. 60—80°) as fawn-coloured needles, m. p. 28°, b. p. 88°/2 mm. (64·0%) (Found: N, 21·8. $C_6H_7N_2F$ requires N, 22·2%), and gave a *hydrochloride*, m. p. 247° (decomp.) (Found: N, 17·2; Cl, 21·7%), glucosazone, m. p. 184° (decomp.), *benzylidene*, m. p. 118° (Found: N, 13·2%), *salicylidene*, m. p. 155° (Found: N, 12·1%), α-*methylbenzylidene*, m. p. 86° (Found: N, 12·2%), and cyclo*hexylidene* derivative, m. p. 41° (Found: N, 13·5%).

*p*-Fluorophenylhydrazine formed nearly colourless needles, m. p. 37·5°, b. p. 95—96°/3 mm. (67·5%), from 1 : 1 ether–light petroleum (b. p. 60—80°) (Found: N, 21·8%). Schiemann and Winkelmüller (*Ber.*, 1933, **66**, 727) give m. p. 39°. It gave a *hydrochloride*, m. p. 200° (decomp.) (Found: N, 17·2; Cl, 21·7%), glucosazone, m. p. 186—187° (decomp.) (*idem, loc. cit.*, give m. p. 187—188°), *benzylidene*, m. p. 140° (Found: N, 13·1%), salicylidene, m. p. 166° (Found: N, 12·0%) (*idem, loc. cit.*, give m. p. 166·5°), α-*methylbenzylidene*, m. p. 107° (Found: N, 12·0%), and cyclo*hexylidene* derivative, m. p. 80—82° (Found: N, 13·3%).

3-*Fluoro*-6-*methylphenylhydrazine.* A Balz–Schiemann reaction with 4-methyl-3-nitro-

aniline yielded **4-*methyl*-3-*nitrobenzenediazonium borofluoride***, m. p. 150—152° (decomp.) (85%) (Found: diazonium N, 10·7. $C_7H_6O_2N_3BF_4$ requires diazonium N, 11·1%). On thermal decomposition it gave 4-fluoro-2-nitrotoluene, b. p. 78°/5 mm. (55%), which was reduced with stannous chloride to 3-fluoro-6-methylaniline, m. p. 37·5°, b. p. 73°/5 mm. (84%) (Found: C, 67·3; H, 6·2; N, 11·2. Calc. for $C_7H_8NF$: C, 67·2; H, 6·4; N, 11·2%). Steck and Fletcher (*J. Amer. Chem. Soc.*, **1948**, **70**, 439) give b. p. 100—101°/16 mm. It gave a ***formyl***, colourless needles (from aqueous alcohol), m. p. 84·5° (Found: N, 9·2. $C_8H_8ONF$ requires N, 9·1%), and ***benzoyl*** derivative, flakes (from ethanol), m. p. 130° (Found: N, 6·0. $C_{14}H_{12}ONF$ requires N, 6·1%). 3-Fluoro-6-methylaniline (12 g.), as described above, gave **3-*fluoro*-6-*methylphenylhydrazine*** (9·2 g., 68·4%), prisms, m. p. 67°, b. p. 112°/3 mm., unchanged when kept for several weeks in the dark (Found: C, 60·3; H, 6·2; N, 19·8. $C_7H_9N_2F$ requires C, 60·0; H, 6·4; N, 20·0%). This formed a hydrochloride, m. p. 190° (decomp.), glucosazone, m. p. 210° (decomp.), ***benzylidene***, m. p. 77° (Found: N, 11·9. $C_{14}H_{13}N_2F$ requires N, 12·2%), ***salicylidene***, m. p. 118° (Found: N, 11·2. $C_{14}H_{13}ON_2F$ requires N, 11·4%), ***α-methylbenzylidene***, m. p. 58° (Found: N, 11·3. $C_{15}H_{15}N_2F$ requires N, 11·5%), and cyclo***hexylidene*** derivative, m. p. 65° (Found: N, 12·6. $C_{13}H_{17}N_2F$ requires N, 12·7%).

The author thanks Dr. F. L. Allen for his interest and support.

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## 665. *The Preparation of* n-*Octadecylamine Hydrochloride.*

By GEOFFREY W. WOOD.

*n*-OCTADECYLAMINE HYDROCHLORIDE has been prepared in excellent overall yield from *n*-octadecyl alcohol, *via* the iodide, by application of the Gabriel synthesis. The method avoids the use of catalytic reduction techniques, and all the reactions may be carried out under ordinary laboratory conditions with simple apparatus.

*Experimental.*—n-***Octadecyl iodide***. To a cooled mixture of "AnalaR" phosphoric acid (45 c.c.) and phosphoric oxide (22 g.), finely powdered potassium iodide (111 g.) and *n*-octadecyl alcohol (90 g.) were added. The mixture was heated in an oil-bath at 110—120°, with stirring, for 5 hr., then cooled, diluted with water, and extracted with ether. The ether extract was washed with aqueous sodium thiosulphate and water and dried ($MgSO_4$), the solvent removed, and the dark brown oily residue dissolved in light petroleum (b. p. 40—50°; 100 c.c.), which solution was chromatographed on activated alumina (370 g.; B.D.H.). Elution with light petroleum (b. p. 40—50°; 750 c.c.) gave *n*-octadecyl iodide (104 g., 85%), m. p. 29—32°; elution with ether–methanol (2 : 1; 1000 c.c.) gave unchanged *n*-octadecyl alcohol (7·3 g.).

N-n-***Octadecylphthalimide***. The iodide (10·2 g.), potassium phthalimide (5 g.), and dimethylformamide (40 c.c.) were heated, with vigorous stirring, in an oil-bath (bath temp. 65—70°) for 1·5 hr. After cooling, the mixture was diluted with water and extracted with chloroform. Removal of the solvent *in vacuo* and crystallisation from ethanol (charcoal) gave N-n-***octadecylphthalimide*** (10·2 g.), white microcrystals, m. p. 75—76·5°. A small amount repeatedly crystallised from ethanol, for analysis, had m. p. 80—81° (Found: C, 78·35; H, 10·55; N, 3·6. $C_{26}H_{41}O_2N$ requires C, 78·15; H, 10·35; N, 3·5%).

n-***Octadecylamine hydrochloride***. A mixture of *N-n*-octadecylphthalimide (10·0 g.), 85% hydrazine hydrate (5·0 c.c.), and methanol (125 c.c.) was heated under gentle reflux on a water-bath for 2 hr. (after 1 hr. a copious precipitate began to form). The methanol was then removed *in vacuo*, and the residue heated under gentle reflux with a mixture of hydrochloric acid (*d* 1·14; 75 c.c.) and water (75 c.c.) for 1 hr. After cooling in ice, the mixture was filtered, the residue digested with hot 95% ethanol (100 c.c.), and undissolved phthalhydrazide (3·0 g.) removed by filtration. The filtrate, on cooling, gave *n*-octadecylamine hydrochloride as large lustrous plates (7·2 g.), m. p. 162—163°. Treatment of an alcoholic solution of the hydrochloride with aqueous calcium picrate afforded the picrate, m. p. 116—117° (Adkins and Billica, *J. Amer. Chem. Soc.*, **1948**, **70**, 695, give m. p. 116°).

The author expresses his sincere thanks to Mr. A. H. Ford-Moore for his interest in this work and to Mr. F. E. Charlton and Miss B. A. Jones for the microanalyses.

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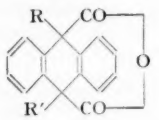
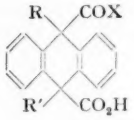
CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT,
PORTON, NR. SALISBURY, WILTSHIRE.

## 666. *Some* 9 : 10-*Dihydroanthracene*-9 : 10-cis-*dicarboxylic Anhydrides.*

By A. H. Beckett, R. G. Lingard, and B. A. Mulley.

During synthesis of anthracene derivatives of possible pharmacological interest, anhydrides (I; R and R′ = H or Me) were required. Only one such has been reported, namely (I; R = R′ = H) (Mathieu, *Ann. Chim.*, 1945, **20**, 215; Rigaudy, *ibid.*, 1950, **5**, 398), and its preparation involved addition of sodium to anthracene, carboxylation and subsequent tedious separation of the mono- and the *trans*- and the *cis*-di-carboxylic acids, followed by the conversion of the latter into the anhydride.

(I) 

 (II)

We have prepared the above anhydrides readily by treatment, with acetic anhydride, of the crude mixed acids resulting from the carbonation of the addition products of the appropriate anthracene derivative and sodium. The separation depended on the stability of the anhydrides at room temperature to dilute sodium hydroxide solution which extracted the unchanged acids from a chloroform solution of the mixture. The m. p. (195—196°) of our anhydride (I; R = R′ = H), even after repeated recrystallisation, was much lower than that reported by Mathieu and Rigaudy (*locc. cit.*); we therefore investigated it in some detail, because the possibility of intermolecular anhydrides exists. (A molecular model shows that the *trans*-dicarboxylic acid cannot form a monomeric anhydride.) Molecular-weight determinations, in conjunction with other evidence, showed that our product is an intramolecular anhydride. Furthermore, opening of the anhydride ring with methyl alcohol gave the monomethyl ester of 9 : 10-dihydroanthracene-9 : 10-*cis*-dicarboxylic acid (II; R = R′ = H; X = OMe) in 70% yield and with a melting point in agreement with that reported by Mathieu for the compound produced from his anhydride. Equivalent-weight determinations of the anhydride, the above monomethyl ester, and the monomorpholide are further proofs of the purity of our anhydride.

The ultra-violet absorption spectrum for 9 : 10-dihydroanthracene-9 : 10-*cis*-dicarboxylic anhydride is typical of that of dihydroanthracene derivatives: there are small maxima at 2640 and 2720 Å (Badger, Jones, and Pearce, *J.*, 1950, 1700; Phillips and Cason, *J. Amer. Chem. Soc.*, 1952, **74**, 2934), and generally feeble absorption (Clar and Wright, *Nature*, 1949, **163**, 921), with virtually none above 2900 Å (Phillips and Cason, *loc. cit.*). A number of authors (Martin, *Ann. combustibles liquides*, 1937, **12**, 97; Badger *et al.*, *loc. cit.*; Takaoka, *J. Faculty Sci., Hokkaido Imp. Univ.*, Ser. III, **3**, 1; *Chem. Abs.*, 1940, **34**, 7888) have reported three small maxima for dihydroanthracene derivatives in the region between 2500 and 2800 Å. However, the third peak, usually around 2550 Å, is probably due to the presence of traces of anthracene derivatives (Phillips and Cason, *loc. cit.*) which absorb much more strongly than dihydroanthracene derivatives. Solutions of 9 : 10-dihydroanthracene-9 : 10-*cis*-dicarboxylic anhydride developed this extra peak on storage for several days.

*Experimental.*—Microanalyses and molecular-weight determinations (ebullioscopic in acetone unless otherwise stated) were by Mr. Crouch, School of Pharmacy, London University. Ultra-violet absorption spectra were measured in ethanol with a Unicam S.P. 500 spectrophotometer.

9 : 10-*Dihydro*-9 : 10-*dimethylanthracene*-9 : 10-cis-*dicarboxylic Anhydride.*—9 : 10-Dimethylanthracene (3·1 g.) (Buu-Hoï, *J. Org. Chem.*, 1951, **16**, 874) in dry benzene (100 ml.) was shaken with finely divided sodium (5 g.) and dry ether (100 ml.) for 48 hr., the yellow solution changing to dark green. The product was slowly added to a large excess of a slurry of solid carbon dioxide in dry ether, excess of sodium destroyed with ethanol, water added, and the organic

layer extracted with dilute sodium hydroxide solution. Acidification of the cold alkaline extract and extraction with ethyl acetate gave crude acids (4·2 g.) on removal of the solvent. These were refluxed with acetic anhydride (10 ml.) for 30 min., chloroform (50 ml.) was added, and the unchanged acids were extracted with dilute sodium hydroxide solution. Evaporation of the chloroform solution after drying ($Na_2SO_4$) gave a solid which was recrystallised from dioxan to give 9 : 10-*dihydro*-9 : 10-*dimethylanthracene*-9 : 10-cis-*dicarboxylic anhydride* (0·5 g., 12%) as colourless, diamond-shaped crystals, m. p. 215—216° (material for analysis was recrystallised from acetic anhydride because the material from dioxan contained solvent of crystallisation : the m. p. was unchanged) [Found : C, 78·0; H, 5·2%; equiv. (refluxing with excess of alkali for 30 min. and back-titration), 138; *M*, 240. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%; equiv., 138; *M*, 278]. Light absorption : Max. at 261 (ε 1320) and 268 mμ (ε 1100).

The *monomorpholide* separated from butanol as plates, m. p. 291—292° (Found : C, 72·0; H, 6·3; N, 3·9%; equiv., 369. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3; N, 3·8%; equiv., 365).

9 : 10-*Dihydroanthracene*-9 : 10-cis-*dicarboxylic Anhydride*.—Anthracene (50 g.; commercial blue fluorescent) was shaken with finely divided sodium (13·5 g.) and glass beads in dry ether (750 ml.) for 4 hr. The resultant blue mixture, treated as above, yielded acids (55 g.) which, after 30 minutes' refluxing with acetic anhydride and subsequent recrystallisation from dioxan, gave 9 : 10-dihydroanthracene-9 : 10-*cis*-dicarboxylic anhydride (14·5 g., 28%) as fine colourless needles, m. p. 194—195° [Found : C, 77·3; H, 4·0%; equiv., 122; *M*, 250, (Rast) 275. Calc. for $C_{16}H_{10}O_3$ : C, 76·8; H, 4·0%; equiv., 125; *M*, 250] (Rigaudy *et al.* give m. p. 233—234°). Light absorption : Max. at 264 (ε 569) and 272 mμ (ε 500).

The *monomorpholide*, prepared in theoretical yield, separated from butanol as colourless crystals, m. p. 222—223° (Found : C, 71·4; H, 5·9; N, 4·3%; equiv., 333. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6; N, 4·2%; equiv., 337). The monomethyl ester had m. p. 181—182° (from butyl ether) (Found : equiv., 143. Calc. for $C_{17}H_{14}O_4$ : equiv., 141) (Mathieu, *loc. cit.*, reports m. p. 178—179°).

9 : 10-*Dihydro*-9-*methylanthracene*-9 : 10-cis-*dicarboxylic Anhydride*.—This *anhydride*, prepared from 9-methylanthracene (Seiglitz and Marx, *Ber.*, 1923, **56**, 1619) by the above method in 25% yield, formed plates, m. p. 222—223° (Found : C, 77·5; H, 4·5%; equiv., 137; *M*, 260. $C_{17}H_{12}O_3$ requires C, 77·2; H, 4·5%; equiv., 132; *M*, 264). Light absorption : Max. at 261 (ε 1140) and 268 mμ (ε 850).

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## 667. *Dimerisation of* 1-*Methylcyclohexene by Formic or Acetic Acid containing Perchloric Acid.*

By George F. Bloomfield.

The addition of formic or acetic acid to many olefins at above 150° has long been known, but the marked catalysis of this reaction by small amounts of perchloric acid is a very recent discovery (Knight, Koos, and Severn, *Chem. Eng. News*, 1952, **30**, 4615). Thus, the hydroxylated derivatives of oleic, elaidic, and linoleic acids, and of methyl oleate, oleyl alcohol, and hex-1-ene are easily and conveniently prepared, via the corresponding formates, in a few minutes at 100°.

*cyclo*Hexene has now been shown to react similarly to produce *cyclo*hexyl formate. With 1-methyl*cyclo*hexene, however, the major product is a hydrocarbon, $C_{14}H_{24}$, which is believed to be 2-methyl-1-1′-methyl*cyclo*hexyl*cyclo*hexene on the basis of the following observations and the assumption of ionic intermediates : (i) molecular weight and empirical formula; (ii) hydrogenation to the saturated hydrocarbon $C_{14}H_{26}$; and (iii) absence of olefinic units detectable by infra-red spectroscopic examination—implying the presence of tetra-substituted ethylenic units. The last feature is consistent with the slow rate of hydrogenation over the particular catalyst used.

The corresponding reactions with acetic acid proceed less efficiently.

*Experimental.—Reactions with* cyclo*hexene*. The two layers initially obtained on adding *cyclo*hexene (10 ml.) to formic acid (90%; 20 ml.) containing perchloric acid (60%; 0·25 ml.) formed a homogeneous brown solution within 20 min. at 100°; this yielded *cyclo*hexyl formate

(11·6 g., 90%), b. p. 48—50°/13 mm. (Found: C, 65·6; H, 9·45%; sap. no., 435. Calc. for $C_7H_{12}O_2$: C, 65·8; H, 9·4%; sap. no., 437), free from higher-boiling contaminants. Reduction of the catalyst concentration by 60% did not diminish the yield of the ester. Replacement of the formic acid by acetic acid gave *cyclo*hexyl acetate (8·6 g., 60%) (Found: C, 67·6; H, 9·95%; sap. no., 394. Calc. for $C_8H_{14}O_2$: C, 67·55; H, 9·9%; sap. no., 400), again free from higher-boiling by-products.

*Reactions with* 1-*methyl*cyclo*hexene*. When 1-methyl*cyclo*hexene (20 ml.) was treated with formic acid (90%; 40 ml.) containing perchloric acid (60%; 0·4 ml.) at 100° the lower acidic layer assumed a deep olive-green colour. After 1 hr. the mixture was poured into water and extracted with ether; the neutralised extract yielded on distillation a little unchanged hydrocarbon together with the following fractions: (i) b. p. 50—65°/13 mm. (4·0 g.); (ii) b. p. 110—125°/13 mm. (8·1 g.); (iii) b. p. 90—110°/0·03 mm. (2·0 g.); (iv) resinous residue (1·0 g.). Fraction (i) was mainly methyl*cyclo*hexyl formate, b. p. 62—64°/15 mm. (Found: C, 68·2; H, 10·0. Calc. for $C_8H_{14}O_2$: C, 67·5; H, 9·85%). Fraction (ii) was oxygen-free and is presumably 2-*methyl*-1-1′-*methyl*cyclo*hexyl*cyclo*hexene*, b. p. 90—92°/2 mm., 58—60°/0·03 mm., $n_D^{20}$ 1·5000 (Found: C, 87·4; H, 12·4%; *M*, 185. $C_{14}H_{24}$ requires C, 87·5; H, 12·5%; *M*, 192). It absorbed 2 atoms of hydrogen per mole during 16 hr. over a palladium–Norit catalyst to give a *dimethyldi*cyclo*hexyl*, b. p. 55°/0·03 mm., $n_D^{20}$ 1·4890 (Found: C, 86·5; H, 13·3%; *M*, 195. $C_{14}H_{28}$ requires C, 86·5; H, 13·5%; *M*, 194). The yellow fraction (iii) was heterogeneous and was divided into (*a*) b. p. 95—106/0·03 mm., $n_D^{20}$ 1·5005 (Found: C, 82·15; H, 11·45%), and (*b*) b. p. 106—110/0·03 mm., $n_D^{20}$ 1·5138 (Found: C, 84·6; H, 11·45%). These products accounted for 80—85% of the original 1-methyl*cyclo*hexene. Use of acetic acid in place of formic acid gave a much more favourable ratio of ester to dimer (2·4 g. and 0·5 g., respectively, from 10 ml. of 1-methyl*cyclo*hexene) but the overall yield of reaction products was low (35% based on olefin used).

This work forms part of the programme of research undertaken by the Board of the British Rubber Producers' Research Association. The author expresses his thanks to Mr. E. S. Waight for spectrographic data and to Dr. W. T. Chambers for microanalyses.

British Rubber Producers' Research Association,
48, Tewin Road, Welwyn Garden City, Herts. [*Received, June 18th*, 1953.]

## 668. *Isolation of a Sulphate of Ruthenium.*

By M. A. Hepworth and P. L. Robinson.

There is no certain evidence that a sulphate of ruthenium has been previously isolated. It is now shown that ruthenium tetroxide and sulphur trioxide react under ultra-violet radiation to give a dark brown solid of the empirical composition represented by ruthenium(VI) oxydisulphate, but which we believe should be formulated as the pyro-salt $Ru(VI)O_2S_2O_7$. The properties of the new sulphate are described.

It appears doubtful whether, in spite of their repetition in most compendia including Sidgwick's "Chemical Elements and their Compounds," Oxford University Press, 1950, p. 1477, any of the alleged isolations of sulphates of ruthenium are well founded. Early work on this theme resulted in the formation of solutions which, somewhat wishfully perhaps, were assumed to contain quadrivalent ruthenium presumably as sulphate. Thus Claus (*J. pr. Chem.*, 1847, **42**, 364), who added a more or less impure ruthenium disulphide [made by precipitating a ruthenium(IV) solution with hydrogen sulphide] to nitric acid, obtained an orange-red solution which he believed to contain the quadrivalent sulphate $Ru(SO_4)_2$. We have found, however, that on evaporation such a solution yields a sticky red mass which we believe to be a complex nitrosyl sulphate. Antony and Lucchesi (*Gazzetta*, 1898, **28**, ii, 139; 1899, **29**, ii, 314) later tried the successive actions of hydrochloric and sulphuric acids on barium ruthenate and obtained a bright red solution which, when treated with sulphur dioxide, became blue, but failed to yield a crystalline sulphate.

Recently, the problem has been approached quantitatively by Martin (*J.*, 1952, 3055),

who showed that the reduction of ruthenium tetroxide in sulphuric acid solution is brought about by a number of reducing agents ranging from $NO_2^-$ to $Fe^{++}$ with the formation, when the ruthenium is below a certain critical concentration, of intensely brown solutions in which the metal had been reduced to the quadrivalent condition. Above this critical concentration the tetroxide gave green solutions in which ruthenium(VI) was shown to be present, most probably, as the ion $RuO_2(SO_4)_2^{--}$, though the instability of this ion at high dilution prevented its being detected in an electrical transference cell. The intermediate 6-valency state was also produced by mixing ruthenium tetroxide with the freshly prepared brown solution, Ru(IV) + Ru(VIII) $\longrightarrow$ 2Ru(VI). Within an hour or two of its preparation, this green solution became brown, probably owing to a disproportionation to quadri- and octa-valent ruthenium.

These interesting reactions appeared to afford little possibility of isolating salts from the necessarily dilute solutions formed in the first instance. The earlier experiments, on the other hand, gave little promise of the successful removal of sulphuric acid from salts which are unstable at temperatures far below those required for this purpose. Wohler, Balz, and Metz (*Z. anorg. Chem.*, 1924, **139**, 213), however, have shown that in aqueous solution ruthenium tetroxide is reduced to the quadrivalent hydrated dioxide by ultraviolet radiation with the simultaneous liberation of oxygen. It therefore seemed worthwhile to study the behaviour of the ruthenium tetroxide–sulphur trioxide system under these conditions. Most interestingly in the light of Martin's work, we find that here again the reduction is to the intermediate sexavalent condition : Ru(VIII) $\longrightarrow$ Ru(VI). Furthermore, after the removal of the excess of sulphur trioxide the residue is a dark brown powder with a composition corresponding to the empirical formula $RuO(SO_4)_2$.

This compound is stable in dry air below about 150°, above which sulphur trioxide is liberated. In moist air it obviously suffers slow hydrolysis, since it then has the characteristic odour of the tetroxide. With water there is instant hydrolysis followed by precipitation of the hydrated dioxide, $RuO_2,xH_2O$. When added, however, to dilute sulphuric acid at room temperature it dissolves, giving the brown colour characteristic of the metal in the quadrivalent state, probably a solution of an oxysulphate of the type Ru(IV)$OSO_4$. Still more interesting is its behaviour on treatment with dilute sulphuric acid at 0°, for then a green solution, evidently the same as observed by Martin (*loc. cit.*), is formed which, as his does, gradually changes colour presumably by disproportionation. The distinctly different behaviour shown towards water and ordinary and cooled dilute sulphuric acid is not unaccountable if it be allowed that the material is pyrosulphate. The vigour of its reaction with a very little water and the liberation of sulphur trioxide in these circumstances make the formulation $Ru(VI)O_2S_2O_7$ probable. The three reactions may then be represented thus: (*a*) With dilute sulphuric acid at 0°, the ion is fixed by an electron transfer from the hydrogen atoms in the reacting water molecule: $Ru(VI)O_2S_2O_7 + H_2O \longrightarrow 2H^+ + Ru(VI)O_2(SO_4)_2^{--}$. (*b*) With dilute sulphuric acid at room temperature, instability is great enough to lead to loss of oxygen: $2Ru(VI)O_2S_2O_7 + H_2O \longrightarrow 2Ru(IV)OSO_4 + 2H_2SO_4 + O_2$. (*c*) With water in large excess the hydrolysis is carried a stage further: $2Ru(VI)O_2S_2O_7 + 4H_2O \longrightarrow 2RuO_2 + 4H_2SO_4 + O_2$.

When fused with potassium hydrogen sulphate part of the ruthenium volatilises as tetroxide and the residual melt is homogeneous, clear, and green. It dissolves in water with formation of a stable bright green solution.

## Experimental

Sulphur trioxide was prepared from fuming sulphuric acid containing 65% of additional $SO_3$ by keeping it over phosphoric oxide for 24 hr. and distilling it. The vacuum apparatus employed was especially dried by flaming it under reduced pressure with a hand torch. When the mixture was warmed, α-sulphur trioxide distilled over as a colourless liquid. It was subsequently subjected to a trap-to-trap distillation with rejection of head and tail fractions before use.

A large excess of the α-sulphur trioxide was distilled in a vacuum on to the dry ruthenium tetroxide contained in a Pyrex bulb cooled with liquid oxygen. The bulb was sealed under

vacuum and the contents were allowed to come to room temperature. As the sulphur trioxide melted, the tetroxide dissolved to an intensely red solution. The bulb and contents were then exposed to ultra-violet light from a lamp kept at such a distance as to hold their temperature at about 40°. After one week the completion of the reaction was made evident by the settling of a dark brown precipitate, leaving the supernatant sulphur trioxide almost colourless. The excess of trioxide was removed at 100° in a vacuum (24 hr.), leaving the *oxysulphate* as a dark brown crystalline solid [Found: Ru, 32·8; $SO_4$, 61·4. $RuO(SO_4)_2$ requires Ru, 32·7; $SO_4$, 62·1%].

The methods of analysis used were: (*a*) Ruthenium by reduction of the compound in dry hydrogen to the metal. Reaction begins about 30° with slight inflammation but thereafter proceeds smoothly. When it was complete, the sulphuric acid and sulphur trioxide liberated were removed by heating in the hydrogen stream preparatory to weighing of the metal. (*b*) Sulphate by adding the compound to excess of 10% aqueous sodium hydrogen carbonate, coagulating the precipitated ruthenium dioxide by boiling for 3 min., and filtering it off, and determining sulphate in the filtrate as barium sulphate.

(*c*) The valency of the ruthenium in the compound was fixed by using Crowell and Yost's method (*J. Amer. Chem. Soc.*, 1928, **50**, 374). A known weight was treated with approx. 50 ml. of 2N-sulphuric acid containing 1 g. of potassium iodide, and the liberated iodine was titrated with 0·1N-thiosulphate in the presence of some carbon tetrachloride to assist in locating the end-point. Three equivs. of iodine were liberated per atom of ruthenium present, and the valency of the ruthenium in the compound is therefore 3 + 3 = 6: $Ru(VI) + 3I^- \longrightarrow Ru(III) + 3I$.

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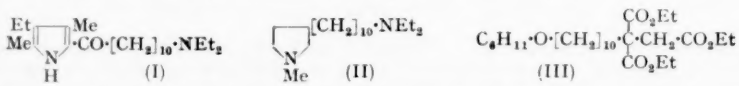
## 669. *Two Basically Substituted Pyrrolidines.*

By JEAN MCCONNEL, VLADIMIR PETROW, and BENNETT STURGEON.

Two open-chain analogues of conessine (Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115) were prepared in order to determine whether the amoebicidal activity of the latter was a function of the steroid nucleus, *per se*, or an expression of a specific biological property often associated with molecules containing two basic centres separated by a polymethylene chain (see, *e.g.*, Hall, Mahboob, and Turner, *J.*, 1950, 1842; 1952, 149, 1956).

2-11′-Diethylaminoundecyl-4-ethyl-3 : 5-dimethylpyrrolidine was synthesised as follows: condensation of 10-diethylaminodecyl cyanide with kryptopyrrolylmagnesium bromide in ethereal solution yielded the ketone (I), which was reduced to 2-11″-diethylaminoundecyl-4-ethyl-3 : 5-dimethylpyrrole by the Huang-Minlon modification of the Wolff–Kishner process (*J. Amer. Chem. Soc.*, 1949, **71**, 3301). The pyrrole ring was then saturated by hydrogenation over Raney nickel. Attempts to extend the synthesis to the use of pyrrolylmagnesium bromide proved unsuccessful.

3-10′-Diethylaminodecyl-1-methylpyrrolidine (II) was prepared by reduction of the corresponding succinimide. The latter was not obtained from 10-diethylaminodecyl chloride as reaction with ethyl sodiomalonate gave too low a yield for the route to be of




value. Condensation of 10-chlorodecanol with ethyl sodiomalonate proved equally unsuccessful, the alkylating agent undergoing resinification. Attention was therefore directed to building up the succinimide ring by employing a terminally-protected decyl halide, followed by replacement of the protecting group by the diethylamino-group.

The readily accessible 10-*cyclo*hexyloxydecyl bromide was condensed with ethyl sodio-

malonate, and the sodio-derivative of the resulting malonic ester alkylated with ethyl chloroacetate to give the tricarboxylic ester (III). Hydrolysis with potassium hydroxide in diethylene glycol at 200°, followed by decarboxylation and dehydration with acetic anhydride, yielded 10-*cyclo*hexyloxydecylsuccinic anhydride. Reaction with methylamine gave the corresponding methylimide, which was reduced to 3-10′-*cyclo*hexyloxydecyl-1-methylpyrrolidine by lithium aluminium hydride. Replacement of the 10-*cyclo*hexyloxy-group was accomplished by successive treatment with concentrated hydrobromic acid and diethylamine; the product (II) was an oil, which formed a characteristic dipicrate.

Only one of the ethoxycarbonyl groups of (III) was hydrolysed by potassium hydroxide at 150°, leading to the substituted ethyl hydrogen malonate. Decarboxylation of this product, followed by reduction with lithium aluminium hydride, yielded 2-10′-*cyclo*hexyloxydecylbutane-1 : 4-diol.

## Experimental

2-11′-*Diethylaminodecyl*-4-*ethyl*-3 : 5-*dimethylpyrrole*.—Kryptopyrrole (25·8 g.) in dry ether (50 ml.) was slowly run into a mechanically stirred solution of ethylmagnesium bromide (from 6·5 g. of magnesium and 23·7 g. of ethyl bromide) in ether (80 ml.) under an atmosphere of nitrogen, and the mixture was heated under reflux for 2 hr. 10-Diethylaminodecyl cyanide (Linnell and Vora, *J. Pharm. Pharmacol.*, 1952, **4**, 55; 25 g.) was added and heating continued for 3 hr. Next morning, the mixture was decomposed by hot 10% ammonium chloride solution during 1 hr. Dilute hydrochloric acid was added, and the unchanged kryptopyrrole extracted with ether. The ketonic product (I) was liberated with sodium hydroxide, isolated with ether, and distilled as a viscous yellow oil (25 g.), b. p. 198°/0·05 mm.

The ketone, 100% hydrazine hydrate (30 ml.), sodium hydroxide (25 g.), and ethyleneglycol (350 ml.) were heated under reflux for 1 hr., and the condenser was then removed. The temperature was raised and maintained at 195°, for 3 hr. The mixture was diluted with water and the product extracted with ether. 2-11′-*Diethylaminodecyl*-4-*ethyl*-3 : 5-*dimethylpyrrole* (18·1 g.) was obtained as a pale yellow oil, b. p. 164°/0·05 mm. (Found: C, 79·1; H, 12·7; N, 8·3. $C_{23}H_{44}N_2$ requires C, 79·3; H, 12·6; N, 8·1%).

2-11′-*Diethylaminoundecyl*-4-*ethyl*-3 : 5-*dimethylpyrrolidine*, prepared by heating the pyrrole in ethanolic solution with hydrogen at 125°/160 atm. for 1 hr. in the presence of Raney nickel W 7, was obtained as an oil (98%), b. p. 145°/0·2 mm. (Found: C, 77·8; H, 13·3; N, 7·7. $C_{23}H_{48}N_2$ requires C, 78·4; H, 13·6; N, 8·0%).

*Ethyl* 10-cyclo*Hexyloxydecylmalonate*.—Sodium (1·47 g.) was dissolved in dry ethanol (62 ml.) and when the solution had cooled to 40°, sodium iodide (0·2 g.) and ethyl malonate (9·35 g.) were added, followed by 10-*cyclo*hexyloxydecyl bromide (Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1536; 18 g.) in small portions. The mixture was heated on the steam-bath for 5 hr. The ethanol was evaporated off and the residue treated with water. *Ethyl* 10-cyclo*hexyloxydecylmalonate* (70%) was extracted with ether, and distilled as an oil, b. p. 172·5°/0·2 mm. (Found: C, 69·1; H, 10·4. $C_{23}H_{42}O_5$ requires C, 69·3; H, 10·6%).

*Ethyl* 12-cyclo*Hexyloxydodecane*-1 : 3 : 3-*tricarboxylate*.—A cold solution of sodium ethoxide [from sodium (1·95 g.) in dry ethanol (87 ml.)] was treated with ethyl 10-*cyclo*hexyloxydecylmalonate (33 g.) and sodium iodide (0·1 g.). After the solution had been shaken for 30 min. ethyl chloroacetate (13 g.) was added, and the mixture refluxed for 15 hr. Isolation of the product gave *ethyl* 12-cyclo*hexyloxydodecane*-1 : 3 : 3-*tricarboxylate* as an oil (Found: C, 66·7; H, 10·4. $C_{27}H_{48}O_7$ requires C, 67·0; H, 10·0%).

10-cyclo*Hexyloxydecylsuccinic Anhydride*.—The foregoing ester (28 g.), diethylene glycol (100 ml.), and 10N-potassium hydroxide solution (60 ml.) were heated without a condenser until the internal temperature reached 200°. The mixture was refluxed for 2 hr. and then poured into 20% sulphuric acid (400 ml.). The resulting acid was extracted with ethyl acetate and decarboxylated at 240° in a metal-bath for 30 min. The residue was heated under reflux with acetic anhydride (100 ml.) for 4 hr. and the product isolated by distillation at 214°/0·3 mm. 10-cyclo*Hexyloxydecylsuccinic anhydride* (31%) solidified on cooling and formed silky needles, m. p. 51°, from chloroform–light petroleum (b. p. 60—80°) (Found: C, 71·1; H, 10·3. $C_{20}H_{34}O_4$ requires C, 71·0; H, 10·3%).

3-10′-cyclo*Hexyloxydecyl*-1-*methylpyrrolidine*.—10-*cyclo*Hexyloxydecylsuccinic anhydride (9·4 g.) and 33% aqueous methylamine (50 ml.) were heated in a metal-bath to 260° (excess of amine evaporating), and then for 30 min. at that temperature. The resulting succinimide was

dissolved in ether and slowly added to a stirred solution of lithium aluminium hydride (5 g.) in ether (400 ml.). The mixture was refluxed for 8 hr. and then decomposed with water, and the product extracted with ether. 3-10′-cyclo*Hexyloxydecyl*-1-*methylpyrrolidine* distilled at 158—162°/0·3 mm. (Found: C, 77·1; H, 12·0; N, 5·2. $C_{21}H_{41}ON$ requires C, 78·0; H, 12·7; N, 4·3%).

3-10′-*Diethylaminodecyl*-1-*methylpyrrolidine*.—The corresponding 10-*cyclo*hexyloxy-compound (4·5 g.) and hydrobromic acid (*d* 1·48; 50 ml.) were boiled for 5 hr., the *cyclo*hexyl bromide being allowed to distil away occasionally. The acid was evaporated and the residue heated at 100° for 20 hr. with diethylamine (10 ml.) and ethanol (20 ml.) in a sealed tube. Dilute alkali was then added and the product extracted with ether and distilled. 3-10′-*Diethylaminodecyl*-1-*methylpyrrolidine* formed an oil, b. p. 140°/0·3 mm. (Found: C, 77·0; H, 13·5; N, 9·4. $C_{19}H_{40}N_2$ requires C, 77·0; H, 13·5; N, 9·5%). The *dipicrate* crystallised in spear-shaped plates (from ethanol), m. p. 140° (Found: C, 49·4; H, 6·2; N, 15·1. $C_{19}H_{40}N_2,2C_6H_3O_7N_3$ requires C, 49·5; H, 5·9; N, 14·9%).

2-10′-cyclo*Hexyloxydecylbutane*-1 : 4-*diol*.—Hydrolysis of ethyl 12-*cyclo*hexyloxydodecane-1 : 3 : 3-tricarboxylate at 150°, followed by decarboxylation of the acid and reduction with lithium aluminium hydride, gave this *glycol* as the main product, b. p. 136—137°/0·2—0·3 mm. (Found: C, 74·9; H, 12·9. $C_{19}H_{38}O_3$ requires C, 75·1; H, 12·6%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this paper.

Chemical Research Laboratories,
The British Drug Houses, Ltd., London, N.1. [*Received, June 24th,* 1953.]

# OBITUARY NOTICE.

## MARGARET LE PLA

1885—1953.

By the death of Margaret Le Pla the Chemical Society has been deprived of the services of a loyal and valued member of its staff; friends have lost a cheery companion; and the science of chemistry has lost an expert indexer of chemical literature. She had been at work until the end of 1952, and was in excellent spirits, although expecting an operation for which she had been receiving preliminary treatment. The operation was most successful, and she insisted on having some indexing material nearby to occupy her time during her recovery. All appeared to be going well, and she was bright and cheerful and talking of return to work. On the morning of January 26th, however, she collapsed, and passed away within a few hours.

Margaret Le Pla was born in Hampstead, on April 17th, 1885, her father, the Rev. Henry Le Pla, being at the time the Minister of Gospel Oak Congregational Church, a post which he held for thirty years.

Her early education was gained at South Hampstead High School; in 1902 she went to Bedford College for Women where she studied chemistry. In 1906 she took her B.Sc. General Degree and was soon appointed a demonstrator. Here she became associated with J. F. Spencer who was also a demonstrator. In collaboration with him she published two papers: "Qualitative separation of thallium from silver" (*J.*, 1908, **93**, 858) and "Eine Elektrode zur Messung der Konzentration der $CO_3''$-Ionen und der Zustand des Silbercarbonats in Lösung" (*Z. anorg. Chem.*, 1909, **65**, 10). One who was a student at Bedford College at that time states that Margaret Le Pla was most generous with her help and was well liked, but, when it was deserved, she did not hesitate to express, with vigour, her unfavourable opinion of the work and behaviour of the students.

Her association with the Chemical Society began in 1910, when J. C. Cain, who was then Editor of its Journal, appointed her as his assistant to index the *Journal*, the *Proceedings*, and the *Annual Reports*. During the remainder of Dr. Cain's life she also prepared indexes for other work in which he was interested. When he died in 1921 her position was placed on a more regular footing by the Chemical Society's appointing her as Indexer. As the editing of the Journal was at that time done at the Editor's home, Miss Le Pla occupied a room adjoining the Reading Room of the Chemical Society's Library. In 1919 the Library hours were extended to eleven hours daily, and the Librarian was permitted to employ her in the Library on one evening weekly and also on certain Saturday afternoons. Her talents were employed here in keeping the subject catalogue up to date and she was well fitted to ensure that the subject headings used were similar to those used in the *Journal* Index. This was an interest which she retained for the rest of her life and gave her great pleasure. She enjoyed meeting the readers, by whom she was well liked, and her assistance was always willingly given when they approached her for help in obtaining information.

When the Fellowship of the Chemical Society was extended to women, Margaret Le Pla was an early applicant, being elected a Fellow on May 5th, 1921, and she became a Life Fellow.

With the formation of the Bureau of Chemical Abstracts in 1924, she became Indexer to its Abstracts and, when the Bureau had obtained premises large enough to house all its staff, she moved from Burlington House, although she could still be found there quite frequently working on the *Journal* index or doing duty in the Library. A few years ago she retired from the service of the Bureau, but retained her post as Indexer of the Chemical Society's publications, and also, after the death of J. N. Goldsmith, undertook the indexing of Thorpe's "Chemical Dictionary." From time to time throughout her career, authors took advantage of her skill to ensure that a book they published had an adequate index.

Her vigorous mind, however, was not content to be only partly employed, and she was delighted when she was invited to re-organize the Research Library of Messrs. C. C. Wakefield & Co. This gave such satisfaction that she was asked to undertake the care of this Library and two or three days weekly were spent on this task, in which she took considerable pleasure.

She was interested in music, and particularly fond of opera. She had a good contralto voice, and studied singing with the late Francis Barrett, then musical critic of the "Morning Post" and through him she heard much of the best of opera and concerts. About 1910 she became a regular member of the Old Vic Opera Company, with whom she sang through the

difficult years, 1914—18, and for some years afterwards, until the increasing demands made on her by her work compelled her to give it up. She used also to arrange amateur concerts, and during World War I she took her party to sing to the sick and wounded.

On her father's retirement, she moved with him to Acton, and when a bomb caused severe damage to the house in 1943 they moved to her brother's home at Ealing, where she spent the rest of her life.

In her later years she was an enthusiastic member of the Women Chemists' Dining Club where she made some good friends, and participation in its functions was one of her greatest pleasures.

Despite the scarcity of her leisure in recent years she greatly enjoyed life; her kindly, generous nature won her many friends who greatly regret her passing but feel that the suddenness with which it came accorded with her wishes, as she never relished the idea of retiring from work.

A. E. Cummins.

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